REPORT

Health Effects Associated with Short-term Exposure to Low Levels of Sulphur Dioxide (SO_2) - A Technical Review

Alberta Health and Wellness

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Health Surveillance

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HEALTH EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO LOW LEVELS OF SULPHUR DIOXIDE (SO_2) -A TECHNICAL REVIEW-

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EXECUTIVE SUMMARY

In response to Recommendations 9 and 59 of the final report of the Provincial Advisory Committee on Public Safety and Sour Gas released in December 2000, Alberta Health and Wellness commissioned reports on the health effects of low-level exposure to hydrogen sulphide (H_2S) and sulphur dioxide (SO_2). The H_2S report on short-term exposure was released in July 2002 (Cantox Environmental, 2002). The present report on SO_2 is the second of four reports. The goal of these reports was to provide a comprehensive review of the available primary scientific literature in order to develop a quantitative understanding of the current state of knowledge with respect to the dose-response relationship between exposure to these contaminants (H_2S and SO_2) and health effects based on the weight of evidence in the peer-reviewed scientific literature. The focus of the third and fourth reports will be on the health effects of chronic exposure to H_2S and SO_2.

The development of the Terms of Reference of the H_2S report was undertaken by an expert panel over a six-month period. The format and goal of this SO_2 report was much the same as the previously completed H_2S report. In addition the Terms of Reference for this report were adopted directly from the H_2S report with few changes. The Terms of Reference state that the focus of this scientific review is to be on the health effects of short-term exposure to SO_2.

The eligibility criteria for the selection of literature were also adopted directly from the H_2S report. The criteria were developed from the Terms of Reference. Only primary studies published in peer-reviewed publications were included in this review. Articles that were not primary scientific studies but were reviews themselves were not included, the primary goal of this review being an unbiased assessment of the scientific literature, not a re-reporting of previously published reviews. Studies reviewed included human clinical studies (clinical), animal toxicology studies (non-clinical), and population studies and case reports (epidemiology). 347 studies satisfied the final eligibility criteria for inclusion in this report, substantially more than for the H_2S report (45 studies) due in part to the inclusion of epidemiology studies.

Each study was critically assessed in terms of technical quality, including experimental design, conduct, and reporting. A level of confidence was assigned to each study based on the technical quality as judged by the reviewing team. The reviewing team consisted of seven members, all with scientific and/or epidemiologic backgrounds and extensive experience critically reviewing scientific literature. Each study was reviewed independently by three members of the reviewing team. The team members followed a pre-defined set of criteria for judging study quality. Of the 347 eligible studies reviewed, 184 (53%) were judged to be of low quality, 150 (43%) were of moderate quality, and only 15 (4%) were of high quality with no major weaknesses in study design or reporting.

The quality ranking of the studies was based on weaknesses or limitations identified by the reviewers. Some of the

more common limitations identified included: too few study subjects, too few exposure concentrations (inability to determine dose-response relationship), failure to follow Good Laboratory Practice guidelines, failure to follow conventional testing protocols, critical information missing on experimental protocols, and unmeasured, poorly measured or unreported exposure concentrations and/or times. In drawing conclusions from this review, emphasis was placed on those studies ranked "high" or "moderate". These studies were judged to have the fewest limitations and therefore provided the strongest and most reliable evidence of association. For some health effects, few moderate or high quality studies were identified.

Results of animal and human studies were evaluated separately. No attempt was made to extrapolate from the animal testing evidence to human effects. It must also be emphasized that this report is a scientific review and as such the interpretations of the science do not represent policy or suggest public health implications.

The greatest number of studies, as well as the greatest number of high and moderate quality studies were those investigating respiratory effects as a result of SO_2 exposure. The strength-of-evidence for respiratory effects provided by these studies confirms that SO_2 exposure under certain conditions (exposure concentration, duration, and breathing method) can adversely affect the respiratory system. Human studies evaluating subjects with bronchopulmonary disease were included as well as those evaluating healthy subjects.

A. Evidence from Human Studies

Two types of studies were evaluated for evidence of effects on humans.

- Clinical studies involved controlled experiments on human volunteers.
- Epidemiology studies investigated short-term changes in health effects in populations with short-term changes in ambient concentration.

Both healthy subjects and those with respiratory illness (asthma or chronic obstructive pulmonary disease) were included in the studies.

Clinical studies covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

The weight of evidence for exposures up to 30 minutes suggests that healthy humans can experience exposures to SO_2 up to 10 ppm with transitory effects[1] on pulmonary function[2], even under challenging conditions involving hyperventilation, mouth-only exposure, and heavy exercise. Transitory effects may be observed at concentrations as low as 0.75 ppm.

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[1] Transitory effects: these effects were observed generally, but not always, for the duration of exposure with functioning returning to normal levels within minutes of hours of cessation of exposure.

[2] Pulmonary function or pulmonary effects: this refers primarily to spirometric changes (e.g. specific airways resistance, forced expiratory volume, etc.) that are measured in a clinical setting. In some cases, pulmonary effects may include clinical symptoms such as bronchoconstriction or throat irritation.

For exposures up to 30 minutes, asthmatics appear to demonstrate pulmonary effects at lower thresholds compared to healthy humans (0.1 ppm). However, even in this population subgroup the clinical effects are transient and may or may not require transient pharmacologic intervention.

The weight of evidence suggests that for single exposures up to 4 hours and repeated exposures between 3 days and 3 weeks, transitory pulmonary effects might occur for asthmatics at exposure concentrations between 0.5 and 1 ppm with exercise and for healthy humans between 0.75 and 25 ppm with exercise, with some evidence for a concentration-dependent response in healthy subjects.

Epidemiology studies were divided into two types based on presentation of exposure concentration. One set of studies calculated exposures as increases in ambient concentration above a baseline or average concentration. The other set of studies reported exposure as discrete concentrations, either as average concentrations or a concentration range.

A weight of evidence evaluation is difficult for the epidemiology studies. This is because the majority of the epidemiology studies (107 of 147) were ranked low quality. For those that ranked moderate quality, there were an equal number of studies that found insignificant or no associations between ambient SO_2 concentration and health outcomes as there were that reported an association.

Deriving causal associations from environmental epidemiologic studies is difficult for a number of reasons. No high quality epidemiology studies were identified. All of the epidemiology studies were subject to substantial limitations due to misclassification of either or both exposure and outcome. The majority of these studies are ecological in nature with outcomes determined on an individual level and exposure determined at a population level. The exposure data collected was generally for ambient levels. Since humans spend a large portion of their time indoors and travel through various microclimates during various activities, ambient levels will likely not provide a good measure of exposure at the individual level. Subsequently, the major weakness observed in these epidemiology studies is the potential for exposure misclassification as a result of the exposure assessment methods. Much of the exposure and outcome data used in these studies is retrospective and from public records, which increases the probability of misclassification due to inconsistent diagnosis of disease status or incorrect assessment of exposure. In addition, many confounding factors cannot be accounted for when using these types of data.

The epidemiology studies also present challenges for interpretation. The different exposure metrics used in the studies makes for difficulty in interpretation. For those studies looking at increases above a baseline, it should be noted that the baseline concentrations differ for each study. The time-averaging or time over which exposure was calculated is different between studies, making comparisons difficult. The populations used tended to be small and relatively undefined. For those studies that did report statistically significant results, the lower confidence intervals

were often very close to one and there were few or no associations where the OR>2.

In addition, SO_2 is just one element in a mixture of pollutants found in "air pollution". It is difficult to isolate the effects of SO_2 from those of other single pollutants or combinations of pollutants. Because of these substantial limitations, the confidence in the results and conclusions from these epidemiology studies could not be judged to be higher than moderate and in most cases the confidence was judged to be low.

There is little reliable evidence in the peer-reviewed scientific literature that meets the terms of reference for this review of human health effects involving the eye, kidney and liver, or the cardiovascular, gastrointestinal, metabolic, immunological, reproductive, or nervous systems. It should be noted that SO_2 is generally considered an eye irritant. However, the conclusion in this report stems from the paucity of good-quality peer-reviewed scientific literature reporting specific effects on the eye. Much of the literature on reproductive effects on humans involves exposures longer than 30 days, which were not covered in this report, but will be covered in subsequent reports.

B. Evidence from animal studies

Much of the animal evidence for respiratory effects concentrates on the mechanisms of action of health effects from SO_2 exposure. Animal studies are also referred to as "**non-clinical**" studies.

As in the human clinical studies, the non-clinical animal studies covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

The concentrations in studies of animals exposed for up to 2 hours ranged between 0.5 ppm and 1000 ppm. For concentrations up to 100 ppm, effects reported were predominantly very mild respiratory effects and changes at the cellular or ciliary level. Above 100 ppm, greater pulmonary effects were in evidence, with indications of changes to the lung. There is evidence of increasing severity of effect with increasing concentration suggesting a possible dose response relationship.

In studies employing exposures between 2 and 24 hours, mild respiratory effects and delayed airway reactivity were reported with concentrations up to 40 ppm. Damage to the lungs was reported at concentrations of 800 ppm and 1225 ppm.

With exposures between 1 and 7 days, slight changes were observed in lung function and in response to virus challenges at concentrations of 0.1 ppm to 34.5 ppm. At the higher concentrations of 100 ppm and 600 ppm, changes to lung structure were reported.

Only five studies investigated exposures between 7 and 30 days. One study reported changes in response to virus challenges with exposures up to 0.1 ppm for 4 weeks. The other four studies reported changes in lung biochemistry and some decrease in pulmonary function at concentrations between 10 and 600 ppm.

Only a few animal studies looked at the effect of SO_2 exposure on the liver or

kidneys. However, there is some evidence of decreased levels of liver lipids and triglycerides and decreased enzyme activity in liver and kidney following continuous SO_2 exposure at 10 ppm for 15 days.
There is some evidence that exposure to SO_2 can affect the metabolic system, in particular lipid metabolism, at exposure times of several days. This effect seems to differ depending on which organ of the body is investigated.

There is some evidence from animal studies that SO_2 exposure both as an adult and prenatally can affect behaviour in adult mice subjected to challenging conditions. There is also some evidence that exposure to SO_2 can affect the lipid content of the brain. The outcomes of both these studies are of unknown clinical significance and the number of studies is limited, although the quality of the studies suggests the results are reliable. It has been established in several species that bronchial restriction upon SO_2 exposure is a reflex reaction; however, the mechanism of this reflex has not been conclusively determined.

In conclusion, there is limited animal evidence with respect to signs and symptoms, or effects on the eye, and reproductive, gastrointestinal, or cardiovascular systems found in the studies reviewed for this report.

TECHNICAL SUMMARY

Background

This report is the second comprehensive literature review commissioned by Alberta Health and Wellness in response to Recommendations 9 and 59 of the final report of the Provincial Advisory Committee on Public Safety and Sour Gas released in December 2000. These recommendations were concerned with the need to advance knowledge of the potential health effects of sour gas exposure. In addition, the Committee recommended that regulations reflect the current knowledge of sour gas and its components.

A comprehensive literature review on the health effects of short-term, low-level exposure to H_2S was released in December 2002 in response to Recommendation 9 (Cantox Environmental Inc., 2002). This review of the health effects of short-term exposure to low levels of SO_2 is in partial fulfillment of Recommendation 59. The H_2S report was prepared by Cantox Environmental Inc. of Calgary.

This current report is a critical review of health effects resulting from SO_2 exposure from published, peer-reviewed sources. Following the mandate of the Provincial Advisory Committee, the review focuses on the health effects of short-term exposures to SO_2. The purpose of this report is to develop a quantitative understanding of the current state of knowledge with respect to the dose-response relationship between exposure to SO_2 and health effects based on the weight of evidence in the peer-reviewed scientific literature.

An expert panel including members of the provincial government, industry, regional health authorities, and other interested stakeholders was convened to provide guidance for the H_2S review. This panel developed the terms of reference and criteria for evaluation of the literature, and provided ongoing guidance during the development of the H_2S review. While the expert panel did not meet regarding the SO_2 report, the Terms of Reference and criteria for evaluation were taken directly from the H_2S review with adaptations as required for SO_2. In addition, members of the panel were given the opportunity to comment and provide advice on the draft versions of this report. In many aspects, this report follows closely the structure and goals of the H_2S review.

The work began in June 2002 with the collection of the literature and was completed in October 2005 with the submission of this final report.

Terms of Reference

The terms of reference for this review are similar to those developed for the H_2S review. As such they are taken directly from the H_2S review, with adaptations as required to address SO_2. Reproductive and developmental effects of SO_2 exposure were not singled out in this report, although they were considered. The limitation to including these studies in this report is that most human studies investigating reproductive effects involve exposure times greater than 30 days. Reproductive effects will be more thoroughly considered in the subsequent report dealing with chronic exposure to SO_2.

The terms of reference, as adapted from the H_2S review for the SO_2 review, are:

- The review was to focus on the health effects following short-term exposure. The term "*short-term*" was to include exposures of both an acute and subacute variety, to capture exposures lasting a few hours to a few days. The subacute category was further defined to include exposures extending up to 30 days.

- The review was to focus on health effects *per se*. Although a formal definition of "*health effects*" was not adopted by the Expert Panel, the meaning was taken to be: *An undesirable or harmful effect on an organism with adverse consequences affecting survival, growth, development, performance, structure and/or function.*

- The review was to be limited to information found in peer-reviewed scientific publications. Preference was to be given to English-language journals.

- The review was to include all currently and readily available journal articles, with a strict need to avoid possible journal and/or sponsor bias.

- The review was to focus on scientific studies involving exposures to SO_2 via inhalation to mimic the expected route of exposure of the general public. Studies involving other routes of exposures (e.g. oral, dermal, injection) were to be excluded from the review.

- The review was to focus on full-length, primary scientific investigations describing original work, rather than on review articles or abstracts.

- The review was to include information from clinical studies involving controlled exposures of human subjects in laboratory settings, non-clinical studies involving controlled exposures of test animals in the laboratory and "population" or epidemiology studies involving exposures following routine or accidental releases of SO_2 into the environment.

- The review was to include a critical assessment of the technical quality of each scientific paper based on consideration of experimental design, conduct and reporting. Judgment of quality was to be based on comparison against testing protocols recommended by leading scientific authorities.

Consistent with the H_2S review, this SO_2 review is strictly a scientific exercise. Only the technical criteria and the scientific meanings of the findings will be presented. Issues of public health implications or policy setting are beyond the scope of this review.

Studies investigating effects on hypersusceptible subjects (those with asthma, chronic obstructive pulmonary disease or hypersensitive airways) were included in addition to those investigating effects on healthy or normal subjects.

The focus of this work was the assessment of the body of scientific knowledge on the potential effects of acute exposure to SO_2 on humans. To that end, human and animal toxicology studies were included in this review. Effects on livestock were not considered.

Methods

As with the H_2S report, work on this report followed several defined stages. The first stage was the literature search. A preliminary search was initiated by Cantox Environmental Inc. The preliminary results formed part of the basis for a more extensive literature search by Alberta Health and Wellness. The purpose of the extensive literature search was to ensure all relevant studies were identified and ultimately included in the final report. Following the search and collection of the literature, a Reference Manager database was created. This served to assign an identifying number to each study for the purposes of the report. The inclusion of key words in the database allowed for the identification of studies focusing on various health effects. The studies were then reviewed following the quality criteria established for the H_2S report. A rating based on the quality criteria (low, moderate or high quality) was assigned to each study by the review team. The next step involved the interpretation of the studies, with the emphasis on studies rated moderate or high.

The search strategy followed for this report was similar to the H_2S search, but more refined with respect to the search terms used. The eligibility criteria for the SO_2 search were the same as for the H_2S search. One difference was the inclusion of epidemiology studies in the SO_2 report. Epidemiology studies investigating a link between short-term changes in exposure and short-term changes in health effects were included in this report. The inclusion of epidemiology studies substantially increased the number of studies included in the SO_2 report compared to the H_2S report. The eligibility criteria for the H_2S search were established by the members of the Expert Panel and reflect the Terms of Reference and were modified for the SO_2 search. The electronic search used the DIALOG Information Retrieval Service.

All studies were entered into a Reference Manager electronic database. In addition to bibliographic information, keywords and the abstracts of all the papers were included. The keywords corresponded to health effects that were to be highlighted in the final report. The unique identifying numbers assigned to the studies as well as the keywords in the database allowed for the easy location of studies pertaining to specific health effects.

347 studies met the eligibility criteria for inclusion in this report. These studies were judged according to pre-defined quality criteria established by the expert panel for the H_2S report. Each study was judged and ranked according to its technical quality as determined by the quality criteria.

A total of seven reviewers made up the reviewing panel for this report. Each paper was reviewed independently by three reviewers, with the goal being to reduce or eliminate reviewer bias. The reviewers represented a variety of scientific and/or epidemiological backgrounds and each had substantial

experience critically reviewing scientific literature.

Other important notes:

- SO_2 is frequently used to induce bronchoconstriction in human and animal studies testing asthma medications. Studies of this type were included if the effect of SO_2 alone could be determined in the study with no interaction with the medication being tested.

- There was no upper limit set for the exposure concentrations used in the studies included in this review in order to provide a complete overview of the scientific literature, and to provide a full picture of the potential health effects of SO_2 exposure.

- Some non-clinical studies report exposure close to chronic exposure (longer than 30 days). These studies were included in this review when effects were reported at time periods shorter than 30 days (i.e. shorter than the full exposure time in the study).

- Some studies report concentrations in units other than ppm or ppb. All units have been converted to ppm or ppb for consistency and to facilitate comparison. The equation used for the conversion was:

  $ppm = mg/m^3 \times 24.45/mol.\ wt.$

  Where:

  24.45 is the volume of 1 mole of air at 25°C and 1 atmosphere; and
  mol. wt. is the molecular weight of $SO_2 = 64.06$

Findings

The 347 studies included in the review were assessed based on their technical quality. Only 15 studies (4%) were judged to be of "high" quality with no major flaws in study design or reporting. 149 studies (43%) were found to be of "moderate" quality with some weaknesses or limitations in either study design or reporting. 183 studies (53%) were judged to have major limitations in study design, conduct, or reporting and were classified as being of poor or "low" quality. Common limitations in those studies rated "moderate" or "low" were very similar to the limitations found in the H_2S literature. Studies covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

A limitation unique to the epidemiology studies is inaccurate or inadequate exposure assessment. This is a common problem in environmental epidemiology. These studies generally compared ambient exposures as measured at monitoring stations with various health effects based on the assumption that ambient monitoring is an accurate description of the exposure of each individual to the contaminants in question. Given that human beings spend a large portion of time indoors, particularly in the Northern Hemisphere, and travel through several microclimates during the course of their various activities, ambient concentrations likely do not accurately reflect SO_2 levels

experienced by individuals. In addition, SO_2 is only one of many compounds in the ambient air. Several studies attempted to account for the influence of other compounds. However, this is a limitation that must be taken into account. Epidemiology studies are vulnerable to exposure misclassification, which consequently weakens confidence in the reported results.
Outcome misclassification is a potential limitation of epidemiology studies using population data for outcome determination. Population data from hospital or medical records may be incomplete and are subject to misclassification or information bias with regards to diagnosis of the disease or cause of death. This is particularly the case for many respiratory diseases that may not have standard case definitions.
Epidemiology studies cannot demonstrate causation, they can only demonstrate association. In other words, epidemiology studies, particularly of the type seen in this review, are hypothesis generating, not hypothesis testing. Epidemiology studies also rely heavily on statistical methods and statistical software to "smooth" the data and identify association. This can result in problems if the software is faulty, for example, the S-Plus issues identified that resulted in the reanalysis of several studies.

Several weaknesses common to many human clinical and animal toxicology (non-clinical) studies included:

- Use of a single exposure concentration, precluding any attempt at determining a dose-response relationship, an important criterion for a causal association.
- Use of a single sex, precluding generalization to a larger population.
- Use of too few test subjects, making it difficult to interpret the significance of test results.
- Lack of routine measures of toxicity, such as signs and symptoms, body weights, and pathology (especially for non-clinical studies). Failure to report these indices makes it difficult to interpret the clinical significance of other observed effects.
- Failure to follow conventional testing protocols and Good Laboratory Practice guidelines.
- Failure to adequately describe exposure conditions, such as concentrations, times, and method of exposure, acclimation protocols (mouthpiece, chamber, etc.).
- Failure to adequately describe characteristics of the test subjects (sex, age, weight, pre-trial health)

Several of the studies, particularly those reviewed in the nervous system, immunological, and respiratory-biochemical effects sections, focussed on the mechanisms of action of SO_2 toxicity. However, the effects were seen at subclinical levels and subsequent clinical repercussions are unclear.

The studies were grouped on a system-by-system basis, following the H_2S report.

Mortality

Clinical Studies
No clinical studies on humans used mortality as a health endpoint, for ethical reasons.

Non-Clinical Studies
Of 7 non-clinical studies investigating mortality of animals, 4 of those were of high or moderate quality. Of those four studies, one high quality study found an increase in mortality rate and decreased survival time of mice with bacterial infections after exposure to 10 ppm SO_2 for one week or longer. However, a moderate quality study reported no change in mortality from bacterial infection in mice exposed to 0.95 ppm for two hours. Two studies observed increases in mortality rates in mice or chickens with increasing exposure time and SO_2 concentration. In mice the SO_2 concentrations ranged from 900 to 1900 ppm for times of 10 to 640 minutes. For chickens, the concentrations ranged from 1 to 5000 ppm for 60 minutes with deaths occurring above 1000 ppm.
One low quality study attempted to determine the LC_{50} in mice at various concentrations and times. However, this study had many limitations, including failure to follow Good Laboratory Practice guidelines.

Epidemiology Studies
Fifty epidemiology studies and case reports were identified that investigated an association between SO_2 exposure and mortality. Only 13 of those studies were evaluated to be of moderate quality. The majority of the epidemiology studies are ecological in nature with outcomes determined on an individual level and exposure determined at a population level. The exposure data collected is generally of ambient levels. Since humans spend a large portion of their time indoors and travel through various microclimates during their daily activities, ambient levels will likely not be a good measure of exposure at the individual level. These studies are subject to the "ecological fallacy" where outcomes and exposures are erroneously ascribed to individuals when only group or population data are available. With the ecological fallacy, an association might be observed on a population level between an outcome and an exposure. However, because of the lack of individual data, we cannot be sure that the individuals who display the outcome are the same individuals who experienced the exposure of interest. Another major weakness observed in these epidemiology studies is the potential for exposure misclassification as a result of the exposure assessment methods. Much of the exposure and outcome data used in these studies is retrospective and from public records, which increases the probability of misclassification bias. Many confounding factors cannot be accounted for when using these types of data.
In addition, SO_2 is just one element in a mixture of pollutants found in "air pollution". It is difficult to isolate the effects of SO_2 from those of other single pollutants or combinations of pollutants. Because of these substantial limitations, the confidence in the results and conclusions from these epidemiology studies could not be judged to be higher than moderate and in most cases the confidence was judged to be low.

The epidemiology studies reported exposure metrics as either incremental

increases in concentration or as absolute concentrations. It is important to keep this distinction in mind when interpreting the results of the studies. With incremental increases in concentration, it is important to be aware that the relative incremental increase occurs in relation to a certain background or average level. For example, when a study reports health effects per 38 ppb increase in ambient concentration, we must understand whether the baseline concentration is 400 ppb or 40 ppb. In other words, are the studies investigating concentrations of 400, 438, 476, and so on or concentrations of 40, 78, 116, etc. This is also important when studies report relative descriptors for exposure concentration increases such as a "doubling" or a "four-fold increase". A doubling of concentration from 4 ppb to 8 ppb will have different implications for human health than a doubling from 400 ppb to 800 ppb. Knowledge of the absolute concentrations will aid in the interpretation of the study results.

Keeping these limitations in mind, general conclusions can be extracted from the moderate quality studies. Several European studies observed an association between incremental increases in SO_2 and daily all-cause mortality for a wide range of baseline concentrations. These studies were part of the APHEA (Air Pollution and Health, a European Approach) project. However, not all of the APHEA studies observed an association between an incremental SO_2 increase and mortality. There was substantial variation in results among the APHEA participant cities. Other studies observed small and sometimes significant associations between a variety of incremental and absolute concentrations and all-cause or cause-specific mortality.

Respiratory System

The majority of studies investigated respiratory health effects related to SO_2 exposure. In addition to these summary paragraphs, please refer to Tables 1 to 9 and Figures 1 to 7.

Clinical Studies

Of the 96 clinical studies investigating respiratory effects, 73 (76%) were ranked high or moderate. Clinical studies covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

There were no high quality studies looking at healthy humans in the time range of 1 to 10 minutes of exposure. There were, however, a number of moderate quality studies. Pulmonary effects[3] in healthy humans starting at 0.75 ppm and up to 15 ppm were observed in clinical studies. These studies involved direct exposure to SO_2 with hyperventilation and/or exercise. There is some evidence that pulmonary effects are greater when exposure is through a mouthpiece (orally) than through the nose. Dryness, irritation and burning of the throat were observed at 3, 15, and 28 ppm in two moderate quality studies.

[3] Pulmonary function, pulmonary effects, or respiratory function: these phrases refer primarily to spirometric changes (e.g. specific airways resistance, forced expiratory volume, etc.) that are measured in a clinical setting. In some cases, pulmonary effects may include clinical symptoms such as bronchoconstriction or throat irritation.

Only one study of 27 investigating exposure of asthmatics for 1 to 10 minutes was rated high quality. This study noted a concentration-dependent change in respiratory function in asthmatics between 0.5 and 1 ppm with exposure to SO_2 during light to heavy exercise. The moderate quality studies also involved direct SO_2 exposure, usually with exercise and/or hyperventilation. Small but significant pulmonary effects were observed in asthmatics at concentrations ranging between 0.1 ppm to 10 ppm. These effects were transitory[4] and pulmonary function returned to normal after exposure ceased. Again, the literature suggests there is evidence that mouth breathing or oral exposure results in greater health effects than nasal exposure.

Pulmonary effects were observed at concentrations as low as 1 ppm at exposures times between 11 and 30 minutes. Again, these effects were transitory. Three studies investigated the effects on cells from the respiratory system after exposure to concentrations between 2.5 and 8 ppm. Some effect was observed on these cells.

Only one study was assessed as high quality for exposures between 11 and 30 minutes. Pulmonary function effects were observed in asthmatics upon exposure to 0.5 ppm SO_2 with moderate exercise.

Other studies suggest pulmonary effects with exercise at concentrations between 0.1 ppm and 1 ppm.

Few studies investigated exposures in asthmatics longer than 30 minutes. Those that did reported transitory pulmonary function effects at exposure levels of 0.50 to 1 ppm. The studies investigating healthy subjects at these longer time ranges investigated concentrations between 0.4 and 25 ppm. A concentration-dependent response in discomfort was reported between 1 and 25 ppm. Transitory effects on pulmonary function and nasal mucous flow were reported up to 5 ppm at these longer time ranges.

The weight of evidence for exposures up to 30 minutes suggests that healthy humans can experience exposures to SO_2 up to 10 ppm with transitory effects on pulmonary function, even under challenging conditions involving hyperventilation, mouth-only exposure, and heavy exercise. Transitory effects may be observed at concentrations as low as 0.75 ppm.
For exposures up to 30 minutes, asthmatics appear to demonstrate pulmonary effects at lower thresholds (0.1 ppm), although even in this population subgroup the clinical effects are transient and may or may not require transient pharmacologic intervention.

The weight of evidence for single exposures up to 4 hours and repeated exposures between 3 days and 3 weeks suggests that transitory pulmonary effects might be expected for asthmatics at exposure concentrations between 0.5 and 1 ppm and for healthy humans between 0.75 and 25 ppm, with some

[4] Transitory effects: these effects were observed generally, but not always, for the duration of exposure with functioning returning to normal levels within minutes of hours of cessation of exposure.

evidence for a concentration-dependent response in healthy subjects.

Of the 93 non-clinical studies investigating respiratory effects, 39 (42%) were ranked high or moderate. These studies looked at a variety of species and health outcomes. In addition there was substantial variation in the concentrations and exposure times investigated. Exposures included single exposures of up to a few hours to several days as well as multiple exposures of a few hours per day for up to 30 days.

The concentrations in studies of animals exposed for up to 2 hours ranged between 0.5 ppm and 1000 ppm. For concentrations up to 100 ppm, effects reported were predominantly very mild respiratory effects and changes at the cellular or ciliary level. Above 100 ppm, greater pulmonary effects were present, with indications of changes to the lung. There is evidence of increasing severity of effect with increasing concentration.

In studies with exposures between 2 and 24 hours, mild respiratory effects and delayed airway reactivity was reported with concentrations up to 40 ppm. Damage to the lungs was reported at concentrations of 800 ppm and 1225 ppm.

At exposures between 1 and 7 days, slight changes were observed in lung function and in response to virus challenges at concentrations between 0.1 ppm and 34.5 ppm. At the higher concentrations of 100 ppm and 600 ppm, changes to lung structure were reported.

Only five studies investigated exposures between 7 and 30 days. One study reported changes in response to virus challenges with exposures up to 0.1 ppm for 4 weeks. The other four studies reported changes in lung biochemistry and some decrease in pulmonary function at concentrations between 10 and 600 ppm.

Of the epidemiology studies and case reports investigating respiratory effects, less than half were ranked moderate. There were no high quality epidemiology studies.
As in the mortality section, epidemiology studies employed two types of metric for exposure concentration. One set of studies calculated exposures as increases in ambient concentration above a baseline or average concentration (incremental). These studies report results as an increase in outcomes (e.g. hospital admissions for asthma) per increase in ambient concentration. For example, a study might report results as a 1.6% increase in hospital admissions for every 3.5 ppm increase in ambient SO_2 concentration. Another set of studies reported exposure as discrete or absolute concentrations, either as average concentrations or a concentration range. These studies might report results as, for example, 7% more admissions during periods of higher pollution.

A weight of evidence evaluation is difficult for the epidemiology studies as the majority of the epidemiology studies were ranked low quality. For the moderate quality studies reporting both types of exposure metric, there was an equal number of studies that found insignificant or no associations between ambient SO_2 concentration and health outcomes as there were that did report an association.

The limitations of the respiratory epidemiology studies are similar to those outlined in the mortality section. Exposure misclassification is a major limitation of these studies. An additional limitation involves the classification of outcome. In several cases, the respiratory diseases investigated, particularly COPD and asthma, did not have clear case definitions for the purposes of the study, which could lead to inaccurate or inconsistent diagnoses of the health outcomes. The issue of incremental and absolute exposure metrics has been discussed. In addition, for those studies looking at increases above a baseline, it should be noted that the baseline concentrations differ for each study. In addition, the time-averaging or time over which exposure was calculated is different between studies, making comparisons difficult. The populations used tended to be small and relatively undefined. Most of the studies endeavored to find correlations between ambient levels of SO_2 and rates of health outcomes. Very few calculated relative risks or similar epidemiological statistics. For those studies that did report statistically significant results, the lower confidence intervals were often very close to one and there were no associations with an OR>2.

Signs and Symptoms

Clinical Studies

Several clinical studies reported signs and symptoms as observations concurrent to investigation of other effects. Healthy subjects reported nose and throat irritation, taste and odour complaints, and discomfort during single exposures (15 and 28 ppm for 10 minutes or less than 1 ppm for 40 minutes) as well as during multiple exposures (1 ppm for 4 hours/day, 3 days/week for 3 weeks and 1 to 25 ppm for 6 hours/day for 3 consecutive days). Some coughing was observed in the healthy subjects during forced mouth breathing. Asthmatic subjects reported chest tightness, shortness of breath, wheezing, asthma symptoms, dyspnea and cough during single exposure both with and without exercise. Concentrations ranged from 0.5 to 1 ppm and lasted between 3 minutes and 3 hours. No symptoms were reported in asthmatics after exposure to 0.5 ppm for one hour, subjects with COPD exposed to 0.8 ppm for one hour, or healthy subjects exposed to 0.15 ppm for 2 hours.

Non-Clinical Studies

Few non-clinical studies reported irritative symptoms as a result of SO_2 exposure. Itching, preening, somnolence, and eye-irritation were observed in guinea pigs exposed to 10 ppm for 1 hour/day for 21 days. Depressed feed and water intake and decreased body weight and oxygen consumption were observed in male mice exposed to 40 ppm for 4 to 11 days. Recovery of body weight and oxygen consumption began immediately after cessation of exposure.

Epidemiology Studies

Shortcomings in epidemiology studies and case-reports have been detailed in the mortality and respiratory summaries of this report. The same limitations apply to the few moderate epidemiology studies and case-reports reporting general signs and symptoms. Responders in a telephone survey during elevated air pollution events with ambient SO_2 levels up to 0.15 ppm reported increased eye and throat irritation, chest discomfort, shortness of breath, and restricted

activity. Two miners exposed to very high concentrations in a mine explosion reported reduced exercise tolerance two years after the accident. No association was reported between ambient SO_2 concentrations up to 3.3 ppm and hospital admissions for asthma, wheeze, or shortness of breath.

Cardiovascular System

There were few studies that investigated the effects of SO_2 on the cardiovascular system including only one moderate quality clinical study. This study reported weak evidence of a difference in electrocardiogram readings after exposure to 0.2 ppm for 1 hour.

Non-Clinical Studies

A high quality non-clinical study reported an increase in the heart rate of chickens with exposure to 5000 ppm for 1 hour, but no effect on heart rate or blood pressure at exposure to 100 ppm for 1 hour. Two moderate quality studies also investigated effects on heart rate and blood pressure. Rats exhibited decreased heart rate after two tidal breaths of 5000 ppm. Geese exhibited increased blood pressure and heart rate with 1 to 3 minutes of exposure to 100 to 400 ppm.

Multiple exposure designs identified decreased glutathione in the hearts of rats (5 to 100 ppm for 5 hours a day for 28 days) and an increase in cholesterol, total lipids, and phospholipids in guinea pig hearts (10 ppm for 1 hour/day for 30 days). The clinical significant of these results is unclear.

Epidemiology Studies

In the lone moderate epidemiology study investigating this system, a small but significant association was reported between daily admission for cardiac disease in London England and Hong Kong and an incremental daily 4 ppb increase (baseline concentrations: 6.8 ± 4.7 ppb) in ambient SO_2 concentrations. The limitations previously identified for epidemiology studies apply to this study. In particular, exposure assessment was a major limitation and the study was rated "moderate-to-low".

Eye

SO_2 is generally acknowledged to have irritant effects on the eye. However, very few studies of the peer-reviewed, scientific studies fitting the terms of reference for this report reported eye effects and none of the studies focussed specifically on investigating eye effects. Some studies with a focus on other health endpoints reported eye effects as a peripheral observation.

Clinical Studies

Of the three clinical studies reporting eye effects, one was rated of high quality while the other two were low quality. The high quality study reported no adverse effects on the eye with exposure to 1 ppm for 4 hours/day, 3 days/week for 3 weeks.

Non-Clinical Studies

The single non-clinical study reporting eye effects was ranked high quality. Eye effects were not a major focus of this study. However, the study reports that exposure of guinea pigs to 10 ppm for 1 hour/day for 12 days leads to signs of eye irritation.

Epidemiology Studies

Only one of four epidemiology studies mentioning eye effects was ranked moderate quality. This study reported

that increases in eye irritation were observed during elevated pollution events with ambient levels up to 0.15 ppm.

Gastrointestinal System

No studies clinical or epidemiology were found that investigated or reported effects to the gastrointestinal system as a result of acute SO_2 exposure.

Non-Clinical Studies

One moderate non-clinical study suggested that inhalation of SO_2 (8.4±0.8, 21±1, and 43±3 ppm) increased levels of lipid peroxidation in stomachs and intestines of male and female mice. These results suggest a toxicological role of SO_2 inhalation on these organs in mice. Confidence intervals were not reported, but Good Laboratory Practice guidelines were generally followed.

General Biochemical Effects

Clinical Studies

Two moderate quality clinical studies were identified. In one study, no association was observed between plasma antioxidant nutrient concentrations and sensitivity to inhaled SO_2. In the other study, a dose-dependent stimulus of reactive oxygen intermediate (ROI) was reported with exposure to concentrations between 0.3 and 1.5 ppm for 30 to 60 minutes. However, it is unclear how much ROI stimulation is required to induce clinically relevant pulmonary fibrosis.

Non-Clinical Studies

Two high quality non-clinical studies were identified. One investigated the effects of SO_2 exposure on serum lipids and lipoproteins and glucose metabolism in diabetic and normal rats. With continuous exposures of 5 and 10 ppm for 15 days, increases in plasma triglycerides and decreases in plasma HDL cholesterol were reported in the healthy rats. Increases in plasma triglycerides and increases in plasma HDL cholesterol were reported in the diabetic rats. The other high quality study investigated responses of chickens to high levels of SO_2 (5000 ppm for 1 hour). Decreased blood pH and increased blood CO_2 were observed. Moderate quality studies reported increased sulfhemoglobin values, and lower whole blood and packed cell viscosity, but no differences in plasma viscosity (0.87 ppm for 24 hours in rats), and a time-dependent decrease in plasma thyroxine levels in mice exposed to 40 ppm for 12 to 24 hours. One study reported no differences in blood variables or hemoglobin affinity in rats exposed to 2 ppm continuously for 1 to 49 days.

No epidemiology studies were identified that fit the criteria for inclusion.

Immunological System

Clinical Studies

Several clinical studies investigated the mechanisms of action of SO_2 on immunological system functions. Increased alveolar macrophage activity was reported in subjects exposed to 4 and 8 ppm for 20 minutes. One study induced rhinovirus infection in a SO_2-exposed group (5 ppm for 4 hours) and a control group. The number of subjects who developed colds was not different between the two groups. However, the SO_2-exposed group experienced a decrease in nasal mucus flow rate, fewer symptoms, and less but more persistent

virus shedding. It has been suggested that mechanisms of asthmatic sensitivity may be associated with a wild-type allele of the TNF-alpha promoter polymorphism or may involve mast cell degranulation.

Non-Clinical Studies

Increased mortality and decreased survival time was observed in a group of female mice with respiratory infection exposed to 10 ppm for up to 3 weeks compared to non-exposed controls. Mice exposed to 0.03 to 0.1 ppm and an influenza virus developed antibodies to the virus more rapidly than mice exposed to the virus alone. The study authors postulate from this that SO_2 alters nasal mucus membranes thereby decreasing a defensive barrier to disease and resulting in increased severity of influenza infection. However, another study reported that exposure to 6 ppm for 7 days resulted in partial inhibition of influenza virus growth in the nasal epithelium and no propagation in the lungs. Studies on guinea pigs suggested that exposure to low levels of SO_2 (1 ppm) might enhance the development of ovalbumin-induced asthmatic reactions and reported a significant increase in ovalbumin-specific antibodies in serum and bronchoalveolar fluid with exposure to 0.1 to 16.6 ppm for 8 hours/day for 5 days. A study on mice exposed to 250 ppm for 3 hours reported an increased uptake of iron in airway epithelium. The clinical significance of many of these studies is unclear and not discussed in the studies themselves.

Epidemiology studies

One moderate quality epidemiology study reported that children with bronchial responsiveness and high serum concentrations of total IgE were particularly susceptible to air pollution, but not SO_2 specifically.

Kidney and Liver

No human clinical or epidemiology studies investigating or reporting liver or kidney effects and fitting the criteria were identified for this review. There were, however, several animal studies.

Non-Clinical Studies

Increases in liver weight and triglycerides in the livers of healthy rats exposed to 10 ppm continuously for 15 days were observed in a high quality study. The same study reported decreased liver weight and a dose-dependent decrease in liver triglycerides in diabetic rats after exposure to 5 or 10 ppm continuously for 15 days. Depletion of phospholipids, cholesterol, cholesterol/phospholipid ratios and lipid peroxidation in guinea pig livers was reported after exposure to 10 ppm for 1 hour/day for 30 days. Glutathione reductase activity was decreased in rat livers at 5 pm for 5 hours/day for 7 to 28 days. In addition, glutathione levels in the liver and kidney were reduced at concentrations between 5 and 100 ppm for the same exposure protocol.

Metabolic System

No human clinical or epidemiology studies were identified that investigated this health outcome and fit the criteria.

Non-Clinical Studies

Continuous exposure of mice to 40 ppm for 4 to 11 days was reported to depress metabolism as measured by oxygen consumption. Decreased enzyme activity was observed in mice (20 ppm for 6 hours/day for 7 days) and rats (5 to 10 ppm for 5 hours/day for 7 to 28 days). Clinical significance of these

observations was not discussed and is unclear.
Changes in lipid metabolism were reported in rats (continuous exposure to 5 and 10 ppm for 15 days) and guinea pigs (20 ppm for 1 hour/day for 30 days).

Nervous System
No human clinical or epidemiology studies were identified as fitting the criteria.

Non-Clinical Studies
Behavioural changes in rearing, social interactions, grooming, digging and chamber-crossing were reported in male and female mice exposed to 5, 12, and 30 ppm of near continuous exposure for 24 days. Male mice exposed to 5, 12, and 30 ppm prenatally exhibited changed aggressive behaviour in adulthood when subjected to an aggressive encounter with an unexposed mouse of the same age, body weight and isolation condition.
Changes in the lipid content of guinea pig and rat brains were reported for exposure to 10 ppm for 1 hour/day for 21 days and 30 days, respectively.
Several studies investigated the effect of SO_2 exposure on respiratory reflex mechanisms. Theses studies concur that the bronchoconstrictive response is reflexive, but the mechanism of the reflex has not been conclusively identified.

Olfactory System
Unlike for H_2S, there are no studies investigating the effect of SO_2 exposure on the sense of smell. Studies concerned with the effects of SO_2 on the nasal passages are described in the section on the respiratory system.

Reproductive System
No clinical studies or moderate or high quality epidemiology studies were identified for this health outcome.

Non-Clinical Studies
No significant teratological or embryotoxicological effects were reported in studies on mice exposed to up to 250 ppm during gestation.
No changes in reproductive performance or neurobehavioral development were reported in male and female mice exposed to up to 30 ppm during gestation. Some social or agonistic behavioural changes were reported during an aggressive encounter in adult male mice that had been exposed to up to 30 ppm during gestation.

Conclusions
The majority of the evidence from the scientific literature reviewed here refers to effects on the respiratory system. There is limited evidence, primarily from animal studies, of effects to other body systems.

Evidence from Human Studies
Both healthy subjects and those with respiratory illness (asthma or chronic obstructive pulmonary disease) were included in this review. The most common effects reported in healthy subjects upon acute exposure to SO_2 include increased airway resistance and bronchoconstriction, decreased maximum expiratory flow, and decreased pulmonary function. Some subjects reported dryness and irritation of the throat, general respiratory discomfort, and unpleasant taste and odours. Effects reported in asthmatic subjects were similar, but also included

increases in asthma symptoms, wheezing, chest tightness, and dyspnea. The weight of evidence suggests that subjects with respiratory illness are more susceptible to respiratory health effects from SO_2 exposure.
Other factors contributing to SO_2-induced effects were examined in these studies. Exercise seems to exacerbate the response to SO_2 in both healthy and asthmatic subjects. Cold and/or dry air also exacerbates the asthmatic response. In addition, the method of exposure affects the response, with forced mouth breathing eliciting a greater response than nasal or oronasal breathing.

Clinical studies covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

The weight of evidence for exposures up to 30 minutes suggests that healthy humans can experience exposures to SO_2 up to 10 ppm with transitory effects on pulmonary function, even under challenging conditions involving hyperventilation, mouth-only exposure, and heavy exercise. Transitory effects may be observed at concentrations as low as 0.75 ppm.
For exposures up to 30 minutes, asthmatics appear to demonstrate pulmonary effects at lower thresholds (0.1 ppm), although even in this population subgroup the clinical effects are transient and may or may not require intermittent pharmacologic intervention.
The weight of evidence for single exposures up to 4 hours and repeated exposures between 3 days and 3 weeks suggests that transitory pulmonary effects might be expected for asthmatics at exposure concentrations between 0.5 and 1 ppm and for healthy humans between 0.75 and 25 ppm, with some evidence for a concentration-dependent response in healthy subjects.

No high quality epidemiology studies or case reports were identified. A weight of evidence evaluation is difficult for the epidemiology studies as the majority of these studies were ranked low quality. For the moderate quality studies reporting both types of exposure metric, there was an equal number of studies that found insignificant or no associations between ambient SO_2 concentration and health outcomes as there were that reported an association. These studies were subject to substantial limitations due to misclassification of both exposure and outcome as well as other limitations outlined previously. Because of these substantial limitations, the confidence in the results and conclusions from these epidemiology studies could not be judged to be higher than moderate and in most cases the confidence was judged to be low.

Associations, when reported, were generally weak. Associations were reported for decreased pulmonary function, and hospital admissions for asthma and other respiratory diseases. Reported symptoms included throat irritation, chest discomfort, restricted activity, shortness of breath, cough, dyspnea, and lower baseline function. Weak associations were reported in epidemiology studies for various mortality causes. However, the body of epidemiological evidence for mortality contains much variability and few studies in which we can have confidence, mainly due to the limitations discussed previously.

There is little reliable evidence in the peer-reviewed scientific literature fitting the terms of reference for this report of human health effects involving the eye, kidney and liver, or the cardiovascular, gastrointestinal, metabolic, immunological, reproductive, or nervous systems.

Evidence from animal studies

Much of the animal evidence for respiratory effects concentrates on the mechanisms of action of health effects from SO_2 exposure. The clinical significance of much of the animal evidence is unclear and was not discussed in the studies themselves.

Studies on respiratory effects were well represented. Reported respiratory effects included increased bronchoconstriction and specific airway resistance and decreased ciliary activity.

Non-clinical studies also covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

The concentrations in respiratory studies of animals exposed for up to 2 hours ranged between 0.5 ppm and 1000 ppm. For concentrations up to 100 ppm, effects reported were predominantly very mild respiratory effects and changes at the cellular or ciliary level. Above 100 ppm, pulmonary effects were more pronounced, with indications of changes to the lung. There is evidence of increasing severity of effect with increasing concentration.

In studies with exposures between 2 and 24 hours, mild respiratory effects and delayed airway reactivity were reported with concentrations up to 40 ppm. Damage to the lungs was reported at concentrations of 800 ppm and 1225 ppm.

At exposures between 1 and 7 days, slight changes in lung function and in response to virus challenges were observed at concentrations between 0.1 ppm and 34.5 ppm. At the higher concentrations of 100 ppm and 600 ppm, changes to lung structure were reported.

Few respiratory studies investigated exposures between 7 and 30 days. One study reported that changes were observed in response to virus challenges with exposures up to 0.1 ppm. The other studies reported changes in lung biochemistry and some decrease in pulmonary function at concentrations between 10 and 600 ppm.

Only a few animal studies looked at the effect of SO_2 exposure on the liver or kidneys. However, there is some evidence of decreased levels of liver lipids and triglycerides and decreased enzyme activity in liver and kidney following continuous SO_2 exposure at 10 ppm for 15 days.

There is some evidence that exposure to SO_2 can affect the metabolic system, in particular lipid metabolism, at exposure times of several days. This effect seems to differ depending on which organ of the body is investigated.

There is some evidence from animal studies that SO_2 exposure both as an adult and prenatally can affect behaviour in adult mice subjected to challenging conditions. There is also some evidence that exposure to SO_2 can affect the lipid content of the brain. The outcomes of both these studies are of unknown clinical significance and, the number of studies is limited, although the quality of the studies suggests the results are

reliable. It has been established in several species that bronchial restriction upon SO_2 exposure is a reflex reaction; however, the mechanism of this reflex has not been conclusively determined.

There is limited animal evidence for signs and symptoms, or effects on the eye, and reproductive, gastrointestinal, or cardiovascular systems found in the animal studies reviewed for this report.

I. BACKGROUND

This report is the second comprehensive literature review commissioned by Alberta Health and Wellness in response to Recommendations 9 and 59 of the final report of the Provincial Advisory Committee on Public Safety and Sour Gas released in December 2000 (ref). These recommendations were concerned with the need to advance knowledge of the potential health effects of sour gas exposure. In addition, the Committee recommended that regulations reflect the current knowledge of sour gas and its components. The two recommendations leading directly to this report and the recently released H_2S report (Cantox Environmental Inc., 2002) are:

Recommendation 9
The EUB work with Alberta Health and Wellness, regional health authorities, Alberta Environment, Alberta Human Resources, industry and other stakeholders to ensure that comprehensive health effects information (qualitative and quantitative) is developed, as soon as practical due to its urgency.

Recommendation 59
The EUB work with Alberta Health and Wellness, regional health authorities and other stakeholders to develop clear requirements and evacuation criteria to address the hazard of SO_2 as a result of ignition.

The comprehensive literature review on the health effects of acute exposure to H_2S was released in December 2002 in response to Recommendation 9 (Cantox Environmental Inc., 2002), hereafter referred to as "the H_2S report". The H_2S report was prepared by Cantox Environmental Inc. of Calgary. The present review of the health effects of acute exposure to low levels of SO_2 is in partial fulfillment of Recommendation 59.

This current report is a critical review of the scientific information on health effects from SO_2 exposure currently available from published, peer-reviewed sources. The purpose of this report is to develop a quantitative understanding of the current state of knowledge with respect to the dose-response relationship between exposure to SO_2 and health effects based on the weight of evidence in the peer-reviewed scientific literature. Following the mandate of the Provincial Advisory Committee, the review focuses on the health effects of acute or short-term exposures to SO_2.

The guidance of the expert panel commissioned for the H_2S report was also applied to this SO_2 report although the expert panel was not specifically re-convened during the initial stages of the SO_2 work. The SO_2 report was modeled on the H_2S report as closely as possible with respect to scope, terms of reference, and criteria for evaluation of the literature. This expert panel for the H_2S report included members of the provincial government, industry, regional health authorities, and other interested stakeholders. The expert panel was asked to comment on draft versions of the report and their input was included in the final version.

The work began in June 2002 with the search and collection of the references and was completed in September 2004 with the submission of this final report.

II. INTRODUCTION

This review is the second comprehensive literature review commissioned by AH&W on the health effects of acute exposure to sour gas components. The first report was the H_2S review that was completed in July 2002 by Cantox Environmental Inc. of Calgary. Work on this SO_2 review began in June 2002. The scope and nature of the H_2S review was defined by an Expert Panel drawn from Alberta Environment, regional health authorities, industry and other interested stakeholders. The terms of reference and scope defined by the Expert Panel in the H_2S review are applied to this SO_2 review.

The structure of the SO_2 report closely follows that of the H_2S report. Selected definitions that are important to ensuring full understanding of the terms of this report were developed in the H_2S report in discussions with the Expert Panel and are adopted here (taken directly from the H_2S report):

short-term, *adj*. **1**. extending over a few hours of a few days. **2**. encompassing acute and subacute events lasting up to 30 days.

health effect, *n*. an undesirable or harmful effect on an organism with adverse consequences affecting survival, growth, development, performance, structure and/or function.

The H_2S report was primarily concerned with exposures below 100 ppm due to the fairly well established results of exposure to high concentrations of H_2S, in particular "H_2S knockdown". However, the effects of exposure to higher levels of SO_2 are not as well characterized. Therefore, no upper SO_2 exposure concentration cut-off was established and studies evaluating higher concentrations of SO_2 are included. These constitute mainly the non-clinical animal trials.

The guidance of the expert advisory panel commissioned for the H_2S report was incorporated into this SO_2 report. The members of the expert panel were:

Dr. Randy Angle
(Alberta Environment)

Mr. Justin Balko
(Alberta Health and Wellness)

Dr. Nicholas Bayliss
(Alberta Health and Wellness)

Dr. Donald Davies ("consultant")
(Cantox Environmental Inc.)

Dr. Stephan Gabos
(Alberta Health and Wellness)

Mr. Geoffrey Granville
(Shell Canada Ltd.)

Mr. Alex MacKenzie
(Alberta Health and Wellness)

Dr. Ingrid Vicas
(Calgary Health Region – Alberta Poison Centre)

Funding for the review team was provided by Alberta Environment.

III. TERMS OF REFERENCE

The terms of reference for this report were modeled after those developed for the H_2S review with changes as required to address SO_2. One exception is the "low-dose" term of reference. As explained previously, exposure concentrations higher than 100 ppm were included in the SO_2 review to capture a complete picture of the potential health effects of SO_2 exposure. In practical terms, only non-clinical animal studies reported measured SO_2 concentrations greater than 100 ppm. Another exception concerns exposure times longer than the defined "short-term" exposure of 30 days or less. Some studies exposed animals for longer time periods. However, if health effects occurred within 30 days, the effects were considered a result of "short-term" exposure and were included in the review.

The terms of reference as outlined in the H_2S report and adapted for the SO_2 report are:

- The review was to focus on the health effects following short-term exposure. The term "*short-term*" was to include exposures of both an acute and subacute variety, to capture exposures lasting a few hours to a few days. The subacute category was further defined to include exposures extending up to 30 days.

- The review was to focus on health effects *per se*. Although a formal definition of "*health effects*" was not adopted by the Expert Panel, the meaning was taken to be: *An undesirable or harmful effect on an organism with adverse consequences affecting survival, growth, development, performance, structure and/or function.*

- The review was to be limited to peer-reviewed, scientific publications. Preference was to be given to English-language journals.

- The review was to include all currently and readily available journal articles, with a strict need to avoid possible journal and/or sponsor bias.

- The review was to focus on scientific studies involving exposures to SO_2 via inhalation to mimic the expected route of exposure of the general public. Studies involving other routes of exposures (e.g. oral, dermal, injection) were to be excluded from review.

- The review was to focus on full-length primary scientific investigations involving controlled exposures of human subjects in laboratory settings, non-clinical studies involving controlled exposures of test animals in the laboratory and "population" studies involving exposures following routine or accidental releases of SO_2 into the environment.

- The review was to include a critical assessment of the technical quality of each scientific paper based on

consideration of experimental design, conduct and reporting. Judgment of quality was to be based on comparison against testing protocols recommended by leading scientific authorities.

A difference between this report and the H_2S report is the inclusion of epidemiology studies in this report. Epidemiology studies investigating a link between short-term changes in exposure and short-term changes in health effects were included in the report. The inclusion of epidemiology studies substantially increased the number of studies included in this report.

Consistent with the H_2S review, *this SO_2 review is strictly a scientific exercise. Only the technical criteria and the scientific meanings of the findings will be presented. Issues of public health implications or policy setting are beyond the scope of this review.*

A large number of studies investigated effects on hypersusceptible subjects (those with asthma, chronic obstructive pulmonary disease or hypersensitive airways). These studies were included in addition to those observing healthy or normal subjects.

The focus of this work was the assessment of the body of scientific knowledge on the potential health effects to humans following short-term exposure to SO_2. To that end, human and animal toxicology studies were included in this review. Effects on livestock were not considered, as they are the subject of a separate review spearheaded by Alberta Environment. The sole exception is two studies on allergic sheep, which were deemed to be of a toxicological nature.

IV. METHODS

As with the H_2S report, work on this report followed several defined stages. The first stage was the literature search. A preliminary search was initiated by Cantox Environmental Inc. The preliminary results formed part of the basis for a more extensive literature search by Alberta Health and Wellness. The purpose of the extensive literature search was to ensure all relevant studies were identified and ultimately included in the final report. Following the search and collection of the literature, a Reference Manager database was created. This served to assign to each study an identifying number for the purposes of the report. The inclusion of key words in the database allowed for the identification of studies focusing on various health effects. The studies were then reviewed following the quality criteria established for the H_2S report. The review team represented a variety of scientific and/or epidemiological backgrounds and each had substantial experience critically reviewing scientific literature. A rating based on the quality criteria (low, moderate or high quality) was assigned to each study by the review team. The next step involved the interpretation of the studies, with the emphasis on studies rated moderate or high.

A. SEARCH STRATEGY

The search strategy was similar to the H_2S search, but more refined with respect to the search terms used, due to the fact that the Term of Reference had been established before the literature search began. A full list of search terms is given in Appendix 2. The eligibility criteria for the SO_2 search were the same as for the H_2S search were established by the members of the Expert Panel and reflect the Terms of Reference. A difference in eligibility criteria for the studies was that in the SO_2 search there was no limit on the exposure concentration. The electronic search used the DIALOG Information Retrieval Service, which includes the following databases:

BIOSIS REVIEWS (1993-2002)
ENVIRONMENTAL BIBLIOGRAPHY (1966 to 2002)
ENVIROLINE (1975 to 2002)
LIFE SCIENCES COLLECTION (1982 to 2002)
MEDLINE (1966 to 2002)
POLLUTION ABSTRACTS (1970 to 2002)
TOXFILE (1966 to 2002)

B. SO_2 DATABASE

To organize and catalogue the large number of studies found in the initial search, all studies were entered into a Reference Manager electronic database. In addition to bibliographic information, keywords and the abstracts of all the papers were incorporated into the database. The keywords corresponded to health effects that were to be highlighted in the final report. The unique identifying numbers assigned to the studies as well as the keywords in the database allowed for the easy location of studies pertaining to specific health effects.

Before entry into the database, studies were subjected to a preliminary assessment as to whether they fulfilled the criteria of acute exposure to SO_2 alone. Studies assessing and reporting the results of SO_2 exposures in combination with other compounds (e.g. PM, smog, etc.) were not included. Each of the 400+ studies in the database were

reviewed independently by three members of the review panel. Upon completion of the detailed review, several studies were found not to conform to the eligibility criteria of the study. Of the over 400 studies entered into the database, 347 were included in the final report.

C. QUALITY CRITERIA

All of the over 400 studies reviewed for this report were assessed against the quality criteria established by the expert panel for the H_2S report. The review templates developed for the H_2S report were used in this review (see Appendix 4). During the review, each study was judged and ranked according to its technical quality as determined by the quality criteria. The ranking categories, also called the "confidence index ranking", were identical to the categories used to rank studies in the H_2S report. The following descriptions of the rankings are taken directly from the H_2S report[5]:

High – Signifying that the study meets or exceeds the recommended guidelines, with no serious weaknesses in experimental design, conduct or reporting. Procedures are well-described and results are properly disclosed to permit meaningful interpretation. Study validity is obvious. Confidence in the findings and conclusions is high.

Moderate – Signifying that the study generally subscribes to the recommended guidelines, but minor deficiencies in design, conduct or reporting detract from the interpretation of the results. Study validity is evident, but not obvious. Careful attention to detail in describing procedures and presenting results and conclusions is somewhat restrained, but not weak.

Low – Signifying that the study fails to meet the recommended guidelines and serious weaknesses in design, conduct and reporting are evident. Significant departures from the recommended guidelines may be present. Sufficient detail is lacking to permit meaningful interpretation of results. Study validity is questionable. Confidence in the findings and conclusions is low."

Of the 347 studies included in the final report, 184 (53%) were rated to be of "low" quality, 149 (43%) were ranked "moderate", and 15 (4%) were judged to be of "high" quality.

D. REVIEW PROCESS

A total of seven reviewers made up the review team for this report. Each paper was reviewed independently by three members of the review team with the goal being to eliminate or reduce reviewer bias. The three reviews for each paper were then combined into a single review. The reviewers represented a variety of scientific and epidemiological backgrounds and each had substantial experience critically reviewing scientific literature. The majority of the reviewers had graduate degrees (Master's level or higher). The papers were assigned to the reviewers in a staggered fashion by study ID such that groups of papers were reviewed by different sets of three reviewers.

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[5] Health Effects Associated with Short-term Exposure to Low Levels of Hydrogen Sulphide (H_2S) – A Technical Review; Cantox Environmental Inc., 2002

OTHER IMPORTANT NOTES:

- SO_2 is frequently used to induce bronchoconstriction in human and animal studies testing asthma medications. Studies of this type were included if the effect of SO_2 alone could be determined in the study separately from the effect of the medication being tested.

- No exposure concentration limit was set on the studies included in this review, with the purpose being to provide a complete overview of the peer-reviewed scientific literature and a full picture of the health effects of SO_2 exposure.

- Some non-clinical studies report exposure longer than 30 days (the cut-off point for "short-term" as defined by the Expert Panel). These studies are included in this review if effects were seen at time periods shorter than the full exposure reported in the study.

- In the H_2S report, human population studies were termed "case-control". In this report, human population studies and case reports are termed epidemiology studies.

- Some studies reported concentrations in units other than ppm or ppb. All units have been converted to ppm or ppb for consistency and to facilitate comparison. The equation used for the conversion was:

  $ppm = mg/m^3 \times 24.45/mol.\ wt.$

  Where:
  24.45 is the volume of 1 mole of air at 25°C and 1 atmosphere; and
  mol. wt. is the molecular weight of $SO_2 = 64.06$

V. SUMMARY OF HEALTH EFFECTS

A. Abbreviations

APHEA = Air Pollution and Health, A European Approach
BAL = bronchoalveolar lavage
COPD = chronic obstructive pulmonary disease
C/P ratio = cholesterol/phospholipid ratio
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
FEF_{25} = maximum flow rate at the last 25% of the vital capacity
FEF_{50} = maximum flow rate at the last 50% of the vital capacity
FRC = functional residual capacity
IP = intratracheal pressure
$MEF_{50\%VC}$ = maximum expiratory flow from one half vital capacity
MMF = maximum mid-expiratory flow
MMFR = maximum mid-expiratory flow rate
NO_2 = nitrogen dioxide
PEF = peak expiratory flow
PM_{10} = particulate matter with an aerodynamic diameter of less than 10 μm
Rl = pulmonary flow resistance
Rn = nasal flow resistance
R_T = total respiratory resistance
SO_2 = sulphur dioxide
$^{35}SO_2$ = radiolabelled SO_2
SRaw = specific airway resistance
V_{max50} = maximum flow calculated at 50% vital capacity
V_{max75} = maximum flow calculated at 75% vital capacity

B. Overview

The goal of this review as laid out in the Term of Reference was to evaluate the scientific literature on health effects of short-term exposure to SO_2. "Short-term" was defined as being from a few minutes to 30 days. Some studies reported exposures lasting longer than 30 days, but with effects apparent in 30 days or less. No upper limit on concentration was set. Only inhalation exposure was considered.

The technical quality of each study was evaluated against pre-determined quality criteria. These quality criteria were developed for the H_2S review and are equally applicable to this review. Since fully transferable criteria from the expert panel were available by which to judge the quality of the SO_2 literature, it was not necessary to develop new criteria for this report.

Each study was reviewed independently by three members of a seven-member review panel. Each member of the review panel conducted their review cogniscent of the need for objectivity, consistency, and fairness.

Each study was ranked according to the level of confidence in the results, also called a "Confidence Index Ranking". This ranking was achieved by a careful evaluation of the strengths and weaknesses of the study. Written summaries of the studies followed a pre-determined format. These written summaries can be found in Appendix 6.

A summary of the health effects of acute exposure to SO_2 is presented in the balance of this chapter. The results are

organized on a system-by-system basis similar to the organization of the H_2S review. In the interpretation of the review results, emphasis was placed on studies ranked "high" or "moderate". Studies ranked "low" were considered to have too many weaknesses in study design or reporting to provide reliable evidence of health effects and were therefore not emphasized in the interpretation.

Confidence Index Ranking
High or high-to-moderate ▲
Moderate-to-high, moderate or moderate-to-low ◆
Low or low-to-moderate ●

The 347 studies included in the review were assessed based on their technical quality. Only 15 studies (4%) were judged to be of "high" quality with no major flaws in study design or reporting. 149 studies (43%) were found to be of "moderate" quality with some weaknesses in either study design or reporting. 183 studies (53%) were judged to have major weaknesses in study design or reporting and were classified as being of poor or "low" quality. Common weaknesses in those studies rated "moderate" or "low" were very similar to the weaknesses reported in the H_2S literature.

Summary tables are provided at the back of this section. These tables list the positive (health outcomes were reported) and negative (health outcomes were not reported) findings presented in the human clinical, non-clinical animal and human epidemiology studies according to the concentrations at which these results were observed. The level of confidence in the findings of each study is indicated. Figures detailing concentration and effect associations at various time intervals are also presented. These tables and figures provide a visual interpretation of the weight-of-evidence provided by the reviewed human clinical and non-clinical animal literature. *These tables and figures do not stand alone and should not be interpreted in the absence of the corresponding written summary.*

No effort has been made to extrapolate results from the animal studies to humans. Such an extrapolation would require knowledge and assumptions beyond the scope of this review of the scientific literature.

C. General Comments

Studies were grouped by study type: human clinical, animal non-clinical, and human epidemiology. Clinical studies were those in which human subjects were exposed to SO_2 under strictly controlled conditions. Non-clinical studies were similar, with the use of animals rather than human subjects. Epidemiology studies included population studies in which the uncontrolled exposure and possibly corresponding health effects of large populations was observed, and case-reports in which very few subjects experienced accidental exposure to high, unmeasured levels of SO_2.

SO_2 is frequently used to induce bronchoconstriction in human and animal studies testing asthma medications. This was the main focus of some of the studies reviewed. These studies were included because the effect of SO_2 alone could be determined in the study separately from the effect of the medication being tested.

Several common weaknesses were observed in the studies reviewed. These weaknesses were very similar to those found in the H_2S literature.

Large numbers of studies used only one concentration. One of the criteria for a causal association between an exposure and an effect is the presence of a dose-response relationship. It is impossible to determine a dose-response relationship from only one exposure concentration. Therefore, these studies had limited contribution to the assessment of SO_2-related health effects.

Many clinical and non-clinical studies tested subjects of only one gender, predominantly males. The use of only one gender limits the generalizability of the results to larger populations.

In many non-clinical studies there was a lack of conventional study designs, particularly Good Laboratory Practices and standard measures of toxicity. None of the studies specifically reported following Good Laboratory Practices. When standard practices are followed, the reliability of and confidence in the results of a study are greatly increased. In addition, interpretation of the clinical significance of observations is facilitated. Many studies failed to report standard measures of toxicity such as signs and symptoms, pathology, and body weights.
The goal of many studies was to investigate the mechanism of action of SO_2 in inducing health effects, particularly with respect to the biochemistry of the respiratory system. These studies reported many results at the subclinical level. The clinical significance of these results is unclear and often not discussed in the individual studies.

Both the epidemiology studies and the case reports showed a general lack of good exposure assessment. Case reports involve traumatic, accidental exposures to high concentrations of SO_2 and as such, accurate exposure concentrations are seldom measured and reported. This makes a quantitative evaluation of the exposure-effect association impossible. However, more qualitative interpretations of these reports can be useful. For example, these reports record severe human health effects observed after exposure to concentrations much higher than would be ethically possible in an experimental situation. The case reports of accidental exposure to "very high" concentrations of SO_2 therefore give us qualitative information on the effects of extreme exposures.
The epidemiology studies are subject to a limitation common to many environmental epidemiology studies: that of inaccurate exposure assessment. Most of the studies reviewed looked at exposure-effect relationships on the most general population level with both exposure and effects identified only for populations, not individuals. In these studies it is impossible to determine whether those individuals presenting with health effects are the same individuals that were exposed. This is called the "ecological fallacy". Other studies evaluated individual health effects, but relied on a few ambient monitors for exposure measurements. Concentrations of air-borne contaminants vary depending on wind speed and direction at any given time, as well as the presence or absence of point sources. Making a link between an individual health effect and this tenuous

measure of individual exposure is difficult. The results of these studies consequently must be evaluated with care.

Please note that the following descriptions of health effects are summaries only. For more detailed information on the design and reporting of the studies reviewed in this report, readers are encouraged to examine the written reviews of individual studies found in Appendix 6 (an electronic attachment).

D. Mortality

Few studies investigated mortality at low levels of exposure. All studies investigating or reporting mortality at all levels of short-term exposure are included here.

Clinical studies

Understandably, no clinical studies investigated mortality outcomes due to ethical considerations.

Non-clinical studies

Azoulay-Dupuis et al. (1982) observed significant increases in mortality rate and significant decreases in survival time in mice with a bacterial infection exposed to 10 ppm SO_2 for durations of one week or longer (Study ID ▲ 172).
Grose et al. (1986) observed no significant change in mortality caused by bacterial infection in mice exposed to 0.95 ppm SO_2 for 2 hours and subsequently challenged with Streptococcus (Study ID ◆ 174).
Bitron and Ahronson (1978) observed increases in percent death in mice during exposure and cumulated mortality with increasing exposure time at concentrations of 900, 1400, and 1900 ppm for exposure times between 10 and 640 minutes (Study ID ◆ 224).
Hilado and Machado (1977) calculated the LC_{50} values for various concentrations and exposure times for Swiss albino mice as: 6800 ppm at 5 minutes, 4400 ppm at 10 minutes, 4000 ppm at 15 minutes and 3000ppm at 30 minutes. However, the number of mice in this study was not clearly reported and the study did not follow Good Laboratory Practice guidelines. (Study ID ● 284).

Asmundsson et al. (1973) observed no increased mortality in hamsters or rats exposed to gradually increasing concentrations up to 400 ppm SO_2 for 5 hours per day, 5 days per week, for 6 weeks. However, in the rats exposed abruptly to 400 ppm, three of 30 rats died in the first 5-hour exposure and 22 of the remaining rats died within the first week of exposure. All six of the hamsters exposed to 400 ppm died in just over 6 hours of exposure (Study ID ● 198).
Cohen et al. (1973) observed decreasing survival time of rats exposed to SO_2 concentrations of 590 ppm and higher with increasing exposure time up to a maximum exposure time of 4 hours (Study ID ● 218).

Fedde and Kuhlmann (1978) exposed chickens to concentrations from 1 to 5000 ppm SO_2 for 60 minutes. Death occurred rapidly in almost all birds at 5000 ppm. However, only two birds in ten died when exposed to 1000 ppm. No deaths were observed at lower concentrations (Study ID ▲ 183).

Epidemiology studies

Many epidemiology studies and case reports have investigated the association

between SO_2 exposure and mortality. Theses studies are summarized in Tables 4A to 4D. The majority of these studies are ecological in nature with outcomes determined on an individual level and exposure determined at a population level. Subsequently, the major weakness observed in these epidemiology studies is the potential for exposure misclassification as a result of the exposure assessment methods. Because of this substantial limitation, the confidence in the results and conclusions from these epidemiology studies could not be judged to be higher than moderate and in most cases the confidence was judged to be low. Many of these studies employed a time-series analysis, meaning that the study was conducted over a period of time. However the focus of these investigations is on short-term changes in SO_2 concentrations (generally, daily) resulting in short-term changes in health status.

All-cause or total mortality

Katsouyanni et al. (1997) pooled the results of the APHEA (Air Pollution and Health, A European Approach) study looking at association between all-cause mortality and concentrations of SO_2 (and other air pollutants) in 12 European cities. Pooled results suggest that a 19 ppb increase in SO_2 is associated with an increase of 3% (95% CI 2% - 4%) in daily mortality in Western European cities and a 0.8% (95%CI -0.1% - 2.4%) increase for central eastern European cities (mean winter SO_2 concentrations 11.4-125.9 ppb). Significant heterogeneity was observed in the SO_2 results (Study ID ◆ 336).

Xu et al. (1994) estimated that the risk of all cause mortality increased by 11% (95% CI 5% -16%) with a doubling of SO_2 concentrations (mean 39 ppb; maximum 240 ppb) in Beijing, China in 1989. A doubling of SO_2 was also associated with significant increases in death from chronic obstructive pulmonary diseases, pulmonary heart disease, and cardiovascular disease (Study ID ◆ 338).

Sunyer et al. (1996) reported that a 38 ppb increase in SO_2 concentrations (in Barcelona, Spain during the period 1985 to 1991 was statistically significantly associated with total mortality (RR 1.13), elder mortality (≥70 years; RR 1.13), and cardiovascular mortality (RR 1.14) for the whole year and the winter, and total mortality, elder mortality, cardiovascular mortality, and respiratory mortality for the summer. SO_2 concentrations ranged in winter from 0.8 ppb-61.1 ppb (mean 17.6 ppb) and in summer from 2.1 ppb-44.5 ppb (mean 13.9ppb). (Study ID ◆ 345).

Touloumi et al. (1996) investigated the effects of short-term effects of "winter type" air pollution (range 2.3 – 138 ppb) on the daily total number of deaths in Athens during 1987 to 1991 as part of the APHEA project. They observed a statistically significant association between SO_2 concentration increases of 38 ppb and a 12% (RR 1.12 (5%CI 1.07-1.16) increased risk of daily mortality (Study ID ◆ 349).

Dab et al. (1996) observed significant associations (RR 1.085 95%CI 1.015-1.159) between mean daily 24-hour SO_2 concentration increases of approximately 38 ppb (above the 5th centile of 2.6 ppb) and daily count of deaths in Paris as part of the APHEA project (Study ID ◆ 351).

Zmirou et al. (1996) investigated the association between daily mortality and ambient air pollution in Lyon, France as part of the APHEA project. Significant associations were observed with a 19

ppb increase in SO_2 (mean 46.76 ppb; range 2.12-315 ppb) for total mortality (RR 1.06 95%CI 1.02-1.09) minus external causes, respiratory deaths, and cardiovascular deaths for the time period between 1985 and 1990 (Study ID ◆ 352).

Using autoregression models, Touloumi et al. (1994) reported a significant association ($p<0.001$) between total daily mortality and the log of air pollution concentrations in Athens, Greece between 1984 and 1988. They state that a 10% reduction in SO_2 would be estimated to decrease mortality by 0.65%. Complete daily data on cause of death and age were not available over the whole period of the study. 24-hour mean SO_2 concentrations were 17±12 ppb (Study ID ◆ 361).

Wietlisbach et al. (1996) investigated the association between mortality and air pollutants in Zurich, Basle, and Geneva, Switzerland between 1984 and 1989. They reported several significant associations with a 3-day moving average of SO_2: total mortality, cardiovascular mortality, and elder mortality (≥65 years) in Basle and Geneva; respiratory mortality in Zurich and Geneva. However, in Basle, the association between SO_2 and mortality was negative at the highest levels of SO_2. Associations and confidence levels were not reported. SO_2 concentrations were: Zurich: 35.4±35.5 ppb, Basle: 26.5±25.3 ppb, Geneva: 40.2±32.7 ppb (Study ID ◆ 403).

Wong et al. (2001) assessed the effects of air pollution on mortality in Hong Kong. Significant associations between SO_2 concentrations and mortality were observed in the cool season (Total mortality RR: 1.04 95% CI: 1.02 – 1.07; Respiratory mortality RR:1.04 95% CI: 1.00 – 1.09; CV mortality RR:1.07 95% CI: 1.02 – 1.11), but not the warm season (Total mortality RR: 1.02 95% CI: 0.99 – 1.04; Respiratory mortality RR: 1.02 95% CI: 0.99 – 1.09; CV mortality RR: 1.01 95% CI: 0.97 – 1.05). This is of interest, because the average SO_2 concentrations were very similar between the two seasons: 6.5 ppb (cool) and 6.9 ppb (warm). This result is explained in the study as the result of greater variability of weather in the warm period and activity differences between the two seasons (Study ID ◆ 464).

Buechley et al. (1973) analyzed deaths in New York and Philadelphia compared to daily SO_2 measurements. They observed an increase in mean mortality residuals with increasing SO_2 concentrations. Mortality excesses of 2% were observed on days when SO_2 concentrations were greater than 190 ppb and mortality was 1.5% less than expected on days when SO_2 levels were below 11 ppb (Study ID ● 012).

Moolgavkar et al. (1995) examined daily mortality and air pollution in Philadelphia between 1973 and 1988. The results indicate that a 100 ppb increase in SO_2 (above daily means of 16.8 ppb (spring) and 25.4 ppb (winter)) is significantly associated with an increase in daily mortality in the spring (RR: 1.19 95% CI: 1.06 – 1.33) and winter (RR: 1.21 95% CI: 1.09 – 1.35), but not in fall (daily mean 17.8 ppb; association not reported) and summer (daily mean 15.7 ppb) (Study ID ● 334).

Spix et al. (1993) investigated daily mortality and air pollution in Erfurt, East Germany between 1980 and 1989. They concluded that effects of SO_2 on mortality are small: 10% excess mortality when comparing the 95% quantile (355 ppb) to the 5% quantile (9 ppb) (RR 1.10; $p<0.01$). The authors

also conclude that SO_2 concentrations likely do not represent personal exposure (mean 75 ppb; range of means 3.8-1361ppb) (Study ID ● 337).

In a paper discussing different predictive epidemiological model building, Spix and Wiehmann (1996) predicted that daily SO_2 mean concentrations between 8 and 47 ppb would result in an increase in daily mortality of 3% for lag day 1 in Köln, Germany (Study ID ● 348).

Glasser and Greenburg (1971) suggest that increases in mortality are associated with increases in ambient SO_2, independent of weather factors in New York City between 1960 and 1964. Differences in mean numbers of deaths were compared between days with SO_2 concentrations of 200 ppb or less and days with 400 ppb or more. Data analysis and exposure assessment are the main limitations of this study (Study ID ● 357).

Krzyzanowski and Wojtyniak (1991) investigated the association between air pollution and daily mortality in Cracow, Poland in the winter months during the period 1977 to 1989. The authors report an association between SO_2 with concentrations greater than 76 ppb, as well as incremental concentration increases of 38 ppb (above 76 ppb; RR=1.19) and daily mortality. No associations were reported at these concentrations in males older than 65 years. However, there are inconsistencies in the reporting, the data analysis is questionable, and confidence intervals are not given, therefore significance cannot be established (Study ID ● 359).

Schimmel and Greenburg (1972) attempted to predict the number of excess deaths attributable to air pollution in New York City during the years 1963 and 1968. They estimate that approximately 20% of the excess deaths could be attributed to SO_2 at concentrations of 17±11 ppb. However, limitations in the analysis and reporting of the data raise questions as to the validity of the results (Study ID ● 366).

Rahlenbeck and Kahl (1996) reported a 4.5% excess mortality in East Berlin in the winters of 1981 to 1989 for increases of 38 ppb SO_2 with means of 41 to 84 ppb. However, limitations of the study design make it difficult to ascertain whether these associations are in fact real (Study ID● 391).

Burnett et al. (1998) investigated the effect of ambient SO_2 on daily mortality from non-accidental causes in 11 Canadian cities. There was little consistency in the relative risks among the cities. The average increased risk of mortality over all the cities from changes in mean SO_2 concentrations (values not given; mean daily concentration 5.4 ppb) was 1.4 %. Confidence intervals and significance were not reported. No information was reported on monitoring systems in each city or the sensitivity of the monitoring instruments, which is important given the low SO_2 concentrations (daily average: 0.7 to 10.5 ppb). The main focus of the study was on mixtures of pollutants, not single pollutants (Study ID ● 395).

Le Tertre et al. (2002) reported significant associations between a 19 ppb increase in SO_2 (baseline exposure not reported) and total mortality (RR: 1.036 95%CI 1.021-1.052), cardiovascular mortality, and respiratory mortality in a study of 9 French cities between 1990 and 1995. There was substantial heterogeneity in the results and the SO_2 concentration measurements among the cities (Study ID ● 407).

Ha et al. (2003) found some positive associations between a 7.8 ppb increase in SO_2 (Mean: 11.1±7.0 ppb Range: 2.4-46.0ppb) and mortality for some age groups. However, these results are presented but not discussed in the study. The focus of this study is PM_{10} (Study ID ● 408).

Botter et al. (2002) observed a significant 2.4 % increase in the daily death count for people over 65 years old in Sao Paulo Brazil between 1991 and 1993 with a 4 ppb increase in SO_2 for a 3-day lag (baseline exposure 1.9-23 ppb). The authors speculate that this effect may reduce the life span of already frail individuals by a few days (Study ID ● 414).

Schwartz et al. (2001) investigated a dose-response relationship between SO_2 and daily mortality in eight Spanish cities. There was a weak association between an increase of 4 ppb SO_2 (baseline exposure 4.2-17 ppb) and daily deaths (0.27%, 95%CI: 0.18-0.73%). However, the risk is not linear with increasing dose and eventually levels off at 20-30 ppb and declines with further increases in concentration (Study ID ● 419).

Small but significant increases in percentage total deaths (RR: 1.0027 95%CI 1.0018-1.0073) were reported with a standard deviation increase in SO_2 concentrations (range 0.3 – 15 ppb) in the summer in Vancouver, British Columbia by Vedal et al. (2003). Similar observations were made in the winter for lag 1. The increases in total deaths were small and confidence intervals were wide. It is speculated that stratification by season may have resulted in a lack of statistical power or that the extensive smoothing of the data affected the associations (Study ID ● 434).

Alberdi Odriozola et al. (1998) found significant associations between a 38 ppb increase in SO_2 concentration (means: 27±20 ppb and 30±17 ppb) and daily mortality. However, the lag times and significance depends on how the data are analyzed with respect to gender, age, season, and cause of death (Study ● ID 465).

Respiratory mortality

Vigotti et al. (1996) observed an increased risk of respiratory death (RR = 1.12, 95% CI 1.03, 1.23) with increased daily SO_2 concentrations of 1 to 316 ppb in Milan, Italy (Study ID ◆ 027).

Zeghoun et al. (2001) observed associations between interquartile increases in SO_2 and respiratory mortality in Rouen, France (IQR increase = 7-14 ppb; Rouen: 8.2% increase 95% CI: 0.4%– 16.6%) and cardiovascular mortality in Le Havre, Franc (IQR increase = 4-13 ppb; 3% increase 95% CI: 0.8% – 5%). Baseline concentrations of SO_2 were: Rouen: Summer: 9.1 ppb, Winter: 13.5 ppb; Le Havre: Summer: 10.6 ppb Winter: 15.1 ppb. Small numbers of deaths were observed and confidence intervals were large (Study ID ◆ 430).

Derriennic et al. (1989) conducted a study in two French cities investigating the possible link between SO_2 air pollution and mortality. They observed a statistically significant association between daily SO_2 concentration and respiratory deaths up to 10 days later in the age group 65 years and older. No relationship was seen between SO_2 concentration at averages of 19 or 25 ppb and cardiovascular deaths (Study ID ● 002).

Hong et al. (1999b) found that SO_2 concentrations above 40 ppb, but not below 40 ppb were a significant

predictor of respiratory mortality with lag day 1, but not with total or cardiovascular mortality in Inchon, Korea over a 20-month period from January 1995 through August 1996 (Study ID ● 412).

Wong et al (2002) observed barely significant associations between a 4 ppb increase in SO_2 (mean 6.4±4.4 ppb) and respiratory mortalities or ischaemic heart disease (RR: 1.015 95% CI: 1.001 – 1.029). The magnitude of the effects was very small (Study ID ● 422).

Venners et al. (2003) observed statistically significant associations between respiratory and cardiovascular mortality and a 38 ppb increase in mean SO_2 concentrations (mean 81.2 ppb) in Chongqing, China in 1995. The associations were strongest on the second and third lag days (Respiratory RR (2d lag): 1.11, 95% CI: 1.02 0 1.22; CV RR (2d lag): 1.10, 95% CI: 1.02 – 1.20; (3d lag): 1.20, 95% CI: 1.11 – 1.30) (Study ID ● 461).

Stroke mortality

Hong et al. (2002b) found significant increased risk (RR: 1.04, 95% CI: 1.01 – 1.08) of ischemic stroke mortality for each interquartile range increase in SO_2 (17.43 ppb; mean 22±19ppb) in Seoul, Korea over a 7-year period (January 1991 to December 1997). However, the results for hemorrhagic stroke mortality were not significant (Study ID ● 397).

Hong et al. (2002a) report a 2.9 % (95%CI: 0.8-5.0%) increase in stroke mortality with a 5.7 ppb increase in SO_2 (Mean: 12.1 ± 7.4) for a 2-day lag in Seoul, Korea. The authors state that it is difficult to determine in this study whether the increase in stroke mortality truly represents an increase of stroke mortality or only an earlier death by a few days or weeks, of those already about to die from previous strokes or other causes (Study ID ● 415).

No association observed

Verhoeff et al. (1996) investigated the association between air pollution and daily mortality in Amsterdam between 1986 and 1992. No association was found between a 38 ppb increase in SO_2 (mean 5 ppb; max. 53 ppb) and daily mortality regardless of lag day (Study ID ◆ 377).

Simpson et al. (1997) observed no significant association between daily mortality and SO_2 concentrations in Brisbane, Australia using the APHEA protocol. SO_2 concentrations were very low (maximum hourly: 60 ppb) (Study ID ◆ 458).

Mazumdar et al. (1982) examine the relationship between daily deaths and daily concentrations of smoke and SO_2 in London, England for the winters of 1958 to 1972. No significant associations were observed per mg/m^3 (380 ppb) increase in SO_2 (range of means: 69-160 ppb) (Study ID ● 332).

Wojtyniak and Piekarski (1996) reported inconsistent associations between SO_2 concentrations (11 to 28 ppb) and cardiovascular mortalities in four Polish cities. Associations were either not significant or significant, but in both directions (positive and negative). These inconsistent results may be a result of exposure and outcome data discrepancies between cities. This is one of the weakest of the APHEA studies (Study ID ● 350).

Bacharova et al. (1996) observed no significant association (Total mortality RR: 0.998; 95% CI: 0.96 – 0.99) between SO_2 concentrations (Winter:16.3±18.1ppb; Spring:7.7±7.2 ppb; Summer:4.5±1.9 ppb; Fall:7.8±6.4 ppb) and daily number of deaths for any

season in Bratislava, Slovak Republic between the years 1987 and 1991. This study followed the APHEA protocol; however, sample size and lack of detail in the reporting limit confidence in these results (Study ID ●354).

Ballester et al. (1996) assessed the short-term relationship between daily air pollution and mortality in Valencia, Spain over the period 1991-1993. No significant results were reported between 4 ppb increases in SO_2 (mean: 15.2±5.9 ppb) and daily mortality (Total mortality RR: 1.007, 95% CI: 0.999 – 1.015; Total mortality (>70yrs) RR: 1.009, 95% CI: 1.00 – 1.21; CV mortality RR: 1.012, 95% CI: 0.995 – 1.026) (Study ID ● 355).

Ballester et al. (2002) investigated the impact of air pollution on mortality in 13 Spanish cities (EMECAM study). For single city analysis, no statistically significant associations were reported between SO_2 concentrations and daily mortality. When the cities were combined, the authors report that a 4 ppb increase in SO_2 (daily mean range: 3.1-17 ppb) is associated with a 0.5% increase in daily deaths; however, there are some inconsistencies in the reporting (Study ID ● 400).

Mackenbach (1993) reported that the positive regression coefficient for the effect of SO_2 on mortality dwindles to zero when all potential confounding factors are taken into account. However, levels of SO_2 measured were reported to be relatively low (range: 5-9 ppb), and the study did not account for the lagged effects of temperature (Study ID ● 356).

Anderson et al. (1996) report a significant association between increased ambient SO_2 concentrations (7-17 ppb) and all-cause mortality in the warm season in London between 1987 and 1992. However, the 95% CI for this association (RR=1.01) includes 1.00 (95%CI 1.00-1.03). No other associations were observed for SO_2 and daily mortality (Study ID ●365).

Kelsall et al. (1997) reported non-significant associations between 12.9 ppb increases in SO_2 concentrations (mean 6.6±4.4 ppb) and total mortality (RR=1.08, 95%CI 0.37-1.78). The focus of this study was TSP rather than SO_2; however, some SO_2 results were reported (Study ID ●389).

In an ecological study, Bobak and Leon (1992) reported a statistically significant association between the highest to lowest quintile for SO_2 (range: <5 to >22 ppb) and post neonatal respiratory mortality. However, confidence intervals included 1 (RR: 3.91 95% CI: 0.90 – 16.9) p=0.062). Only weak, non-significant associations were reported for other infant mortalities (Study ID ● 440).

Saldiva et al. (1994) observed no association between SO_2 concentrations (mean: 6 ±4 ppb) and respiratory mortality in children in Sao Paulo, Brazil for the period May 1990 to April 1991 (Study ID ● 442).

Kinney and Ozkaynak (1991) observed no association between changes in SO_2 concentration (mean 15 ± 6 ppb) and mortality in Los Angeles County, California for the time period 1970 to 1979 (Study ID ● 443).

Kotesovec et al. (2000) found no association between daily total mortality and 38 ppb increase in SO_2 concentrations (mean 38±34 ppb) for the entire population of Northern Bohemia when gender, age, and cause of death were not separated out. In the over 65 years age group, higher daily cancer mortality rates in males were associated with increased SO_2 concentrations (Study ID ● 479).

Hong et al. (1999a) investigated the association between total daily mortality or cardiovascular mortality and air pollution, including TSP, PM_{10}, SO_2, NO_2, O_3, and CO in Inchon, Korea. Relative risks for an increase of 4 ppb in SO_2 (mean 22.6 ppb) were not significant for either total or cardiovascular mortality (Total mortality RR: 1.007, 95% CI: 0.56 – 1.062; CV mortality RR: 1.028, 95% CI: 0.937 – 1.129) (Study ID ● 480). Schwartz and Dockery (1992) investigated the association between total mortality and total suspended particulates (TSP) and SO_2 in Philadelphia. Deaths from accidents and deaths outside the city were excluded and possible confounders such as year, season, temperature, and humidity were controlled for. A significant positive association was observed between total mortality and SO_2 for both current day and prior day SO_2 measurements. Total mortality was estimated to increase by 5% with each 38 ppb increase in SO_2 (mean: 21 ppb). However, when TSP and SO_2 were considered simultaneously, the SO_2 association was no longer significant (Study ID ● 483).

Case-studies

A few studies investigated industrial accidents where humans were exposed to extremely high levels of SO_2 in catastrophic circumstances. Exposure concentrations are generally not measured in these situations. Harkonen et al. (1983) report the experiences of seven men accidentally exposed to high concentrations of SO_2 in a pyrite mine explosion. Exposure concentrations are unknown and duration of exposure was estimated at 20 to 25 minutes. Nine men were initially exposed. Two subsequently died. (Study ID ● 021). A case report (Charan et al., 1979) describes an industrial accident in which five men were exposed to very high, but unmeasured, concentrations of SO_2. Two of the men died and the short-term and long-term symptoms of the remaining three men are described in detail (Study ID ● 270).

Summary:

Clinical

No clinical studies used mortality as a health endpoint, for ethical reasons.

Non-Clinical

There are few high or moderate ranked non-clinical studies on mortality. Of those, one high quality study found an increase in mortality rate and decreased survival time of mice with bacterial infections after exposure to 10 ppm SO_2 for one week or longer. However, a moderate quality study reported no change in mortality from bacterial infection in mice exposed to 0.95 ppm for two hours. Two studies observed increases in mortality rates in mice or chickens with increasing exposure time and SO_2 concentration. In mice the SO_2 concentrations ranged from 900 to 1900 ppm for times of 10 to 640 minutes. For chickens, the concentrations ranged from 1 to 5000 ppm for 60 minutes with deaths occurring above 1000 ppm. One low quality study attempted to determine the LC_{50} in mice at various concentrations and time. However, this study had many limitations, including failure to follow Good Laboratory Practice guidelines.

Epidemiology

Many epidemiology studies and case reports investigated an association between SO_2 exposure and mortality.

The majority of these studies are ecological in nature with outcomes determined on an individual level and exposure determined at a population level. The exposure data collected is generally of ambient levels. Since humans spend a large portion of their time indoors and travel through various micro-climates during their daily activities, ambient levels will likely not be a good measure of exposure at the individual level. Subsequently, the major weakness observed in these epidemiology studies is the potential for exposure misclassification as a result of the exposure assessment methods. Much of the exposure and outcome data used in these studies is retrospective and from public records, which increases the probability of misclassification and bias. Many confounding factors cannot be accounted for when using these types of data.
In addition, SO_2 is just one element in a mixture of pollutants found in "air pollution". It is difficult to isolate the effects of SO_2 from those of other single pollutants or combinations of pollutants. Because of these substantial limitations, the confidence in the results and conclusions from these epidemiology studies could not be judged to be higher than moderate and in most cases the confidence was judged to be low.

Keeping these limitations in mind, general conclusions can be extracted from the moderate quality studies. Several European studies observed an association between in increase of 38 ppb SO_2 and daily all-cause mortality. These studies were part of the APHEA (Air Pollution and Health, a European Approach) project. One of the APHEA studies, however, observed no association between a 38 ppb increase and mortality. There was substantial variation in results among the APHEA participant cities.
Other studies suggest an association between SO_2 concentrations ranging from 19 and 41 ppb and daily all-cause mortality. An Australian study observed no association between daily mortality and SO_2 in Brisbane with maximum hourly concentrations of 60 ppb.
Other studies observed small but significant increases in respiratory mortality in Milan (1-316 ppb) and Rouen, France (increase from 7 to 14 ppb).

E. Respiratory System

Please refer to Tables 1 to 9 and Figures 1 to 7 for further summary of the information in the following section.

Respiratory System - Functional

Clinical studies
Numerous clinical studies investigated the effects of acute SO_2 exposure on respiratory function. These studies have been arranged in subcategories for clarity and comparison.

Adolescents
One group, Koenig et al., carried out a suite of studies investigating the respiratory effects of SO_2 on adolescents. In one study, (Koenig et al., 1982a) eight adolescents with signs of hyperactive airways but no clinical diagnosis of asthma were exposed to 1 ppm SO_2 for 30 minutes at rest and 10 minutes while exercising. Baseline function values did not change significantly. However, statistically significant reductions (24 to 34%) were observed in FEV_1, V_{max50}, and V_{max75} after exercise (Study ID ◆ 038).

In a related study (Koenig et al., 1982b), healthy adolescents were exposed to SO_2 using the same exposure protocol. No statistically significant changes to pulmonary function parameters were observed after exposure at rest. Slight, but statistically significant reductions were observed in FEV_1, V_{max50}, and V_{max75} after exercise (Study ID ◆ 042).
In a further study (Koenig et al., 1985), asthmatic adolescents were exposed to 0.5 ppm SO_2 for 50-minute periods on five separate days to investigate the relationship between changes in nasal power and pulmonary function depending on the route of exposure to SO_2 (oral or oronasal). Statistically significant changes (16-69%) in total respiratory resistance, FEV_1, V_{max50}, and V_{max75} were observed for all routes of exposure. In addition, changes in FEV_1 and V_{max50} were greater after oral inhalation compared to oronasal inhalation (Study ID ◆ 099).
The research group (Koenig et al., 1987) exposed asthmatic adolescents to 0.75 ppm for 10 minutes during exercise and observed a statistically significant decrease in FEV_1 and an increase in total respiratory resistance (Study ID ◆ 103).
In a similar study (Koenig et al., 1989), asthmatic adolescents were exposed to 1.0 ppm SO_2 for 10 minutes during exercise (Study ID ◆ 102). Results were similar to those observed in Koenig et al. (1987) (Study ID ◆ 103).
Finally, adolescent asthmatics were exposed to 100 ppb SO_2 for 15 minutes and a slight decrease in FEV_1 and V_{max50} was observed (Koenig et al., 1990; Study ID ◆ 277).

Effects observed-healthy subjects
A multitude of studies reported SO_2-induced effects on pulmonary function in healthy subjects.
Stacy et al. (1981) exposed healthy male subjects to 0.75 ppm SO_2 for 2 hours with one 15-minute exercise period while measuring a variety of pulmonary function parameters. Only airway resistance was significantly changed by exposure to SO_2. Subjects who responded to allergen skin tests were also found to be significantly more reactive to SO_2 than subjects who did not respond to allergen skin tests (Study ID ▲ 060).
Kulle et al. (1986) observed small but statistically significant decreases in spirometric function after exposure to 1 ppm SO_2 for 4 hours per day, three days per week for 3 weeks in healthy adults (Study ID ▲ 096).
Newhouse et al. (1978) exposed healthy adults to 5 ppm SO_2 for 2.5 hours and assessed pulmonary function. They observed a significant decrease in maximum mid-expiratory flow rates and a significant increase in bronchial clearance. No changes in FEV_1 were observed (Study ID ◆ 045).
Bedi et al. (1984) investigated the threshold concentration of SO_2 for pulmonary function changes by exposing healthy adult males to 1 to 2 ppm for 2 hours during which time there were three 30-minute exercise periods. The only significant change observed was an increase in specific airway resistance (SRaw) at both concentrations. No changes were observed in other pulmonary function parameters (Study ID ◆ 047).
Wolff et al. (1975) exposed healthy adults to 5 ppm SO_2 for 3 hours and measured pulmonary function parameters. They observed a significant decrease in maximal midexpiratory flow (Study ID ◆ 056).
Snell and Luchsinger (1969) exposed healthy adults to 0.5, 1, and 5 ppm SO_2

for 15 minutes after a 15-minute control period. They observed a significant decrease in maximum expiratory flow from one half vital capacity ($MEF_{50\%VC}$) at 1 and 5 ppm exposure levels. More exposures at 5 ppm for 15 minutes were done either through a mask or a mouthpiece. Average $MEF_{50\%VC}$ was higher with mask rather than mouthpiece exposure. A reduction in conductance was observed with both exposure methods (Study ID ◆ 070).

Kagawa (1983) exposed healthy adult males to 0.15 ppm of SO_2 for 2 hours. A significant decrease in specific airway conductance was observed in just over half the subjects during exposure. Significant increases were observed in functional residual capacity and residual volume (Study ID ◆ 072).

Andersen et al. (1974) exposed a small group of healthy adults to SO_2 concentrations of 1, 5, and 25 ppm for 6 hours a day for 3 consecutive days. A significant decrease in nasal mucus flow rate was observed at 5 and 25 ppm. In addition, increased nasal airflow resistance was observed at all concentrations. No change in closing volume was observed (Study ID ◆ 063).

Islam et al. (1994) exposed 37 healthy, nonsmoking volunteers to 0.73±0.05 ppm of SO_2 or cold air for 5 minutes and observed airway response. A statistically greater increase in SRaw was observed after hyperventilation with SO_2 than after hyperventilation with cold air (Study ID ◆ 318).

Andersen et al. (1977) induced rhinovirus infection in normal adults both with and without previous controlled SO_2 exposure. The group exposed to 5 ppm SO_2 for 4 hours was found to have fewer symptoms of infection than the unexposed group. However, there was no difference in the number of subjects who developed infection between the SO_2-exposed and unexposed groups. The only difference between the two groups was a decrease in nasal mucus flow rate in the anterior parts of the nose in the SO_2-exposed group (Study ID ◆ 048).

Nadel et al. (1965) exposed healthy adults to 4 to 6 ppm SO_2 for 10 minutes. They observed significant decreases in airway conductance and thoracic gas volume after exposure (Study ID ● 069).

In a study by Frank et al. (1964), healthy male adults were exposed to three levels of SO_2: 1-2 ppm, 4-6 ppm, and 14-17 ppm for 30 minutes. No change in pulmonary flow resistance was observed at the lowest exposure. Some increase in pulmonary flow resistance was observed at the middle exposure, and an even greater increase was observed at the highest exposure (Study ID ● 076).

Frank et al. (1961) exposed 11 healthy adult male volunteers to 1, 5, and 13 ppm SO_2 to investigate the effect on pulmonary flow resistance. There seemed to be a dose-response trend with some of the volunteers. Most of the results in this study were not significant and there was substantial variability among the volunteers (Study ID ● 323).

Douglas and Coe (1987) discovered that the threshold concentration of SO_2 required to induce lung effects (1 ppm) is less than that required to induce eye effects (5 ppm) (Study ID ● 121).

Amdur et al. (1953) observed decreased tidal volume and increased respiratory and pulse rates in healthy subjects exposed to 1 to 8 ppm SO_2 for 10 minutes (Study ID ● 032).

Lawther et al. (1975) exposed healthy adults to SO_2 concentrations ranging from 1 to 30 ppm in a variety of experiments involving both deep and shallow breathing for durations of 10

minutes to one hour. Small but significant changes in SRaw were observed following hyperventilation of 1 ppm, for an undetermined period of time. Significant changes in response were observed for most, but not all, of the subjects after "quiet breathing" of 10, 15, 20, and 30 ppm for 10 minutes at each concentration. No significant changes were observed for normal breathing at 1 ppm and were varied for deep breathing at 3 ppm. The numbers of subjects varied for each part of the experiment, exposure method varied for each experiment and exposure durations are not always clearly stated in the paper. Not all of the experiments were blinded, and some of the subjects were smokers (Study ID● 317).

Sim and Pattle (1957) exposed healthy male adults to various aerosol and gas mixtures by mask and in a chamber. Maximum dosages were 2160 mg min/m^3 (mask) and 3620 mg min/m^3 (chamber). No effects were observed at dosages below 800 mg min/m^3. Above 1300 mg min/m^3, resistance to air flow was significantly increased in half the volunteers receiving exposure both by mask and by chamber. At this dosage and higher, high-pitched musical rales were observed with a tendency to prolongation of the expiratory phase of respiration. However, sample size was not given and exposure levels and number of exposures for each volunteer were not clearly stated (Study ID ● 324).

Whittenberger and Frank (1963) exposed work colleagues to 1, 5, and 13 ppm for an unidentified amount of time. The health status of the volunteers is unknown, but was assumed to be healthy, except for one subject with a history of childhood asthma. Increases in airway resistance were observed at 5 and 13 ppm for the group, with the exception of the childhood asthma case, who showed airway resistance at 1 ppm. The reported details of this study were limited and unclear (Study ID ● 416).

No effect observed-healthy subjects

Several studies observed no effects on respiratory function in either healthy or asthmatic subjects as a result of exposure.

Stacy et al. (1981) exposed healthy adult males to 0.75 ppm SO_2 for four hours. Each four-hour exposure session included two 15-minute periods of controlled moderate exercise. Nineteen different pulmonary function measurements were taken just prior to exposure, two and four hours into exposure, following each exercise session during exposure, and 24 hours after the exposure. They observed no statistically significant effects in any of the pulmonary function measurements during or after exposure to SO_2 (Study ID ▲ 043).

Kreisman et al. (1976) evaluated the respiratory function of healthy adults breathing 0.5 to 5 ppm SO_2 by mouth for 1 to 5 minutes. They observed variable airway response to SO_2 exposure and were not able to determine a dose-response relationship with increasing concentration or time of exposure (Study ID ◆ 039).

Bedi et al. (1979, 1982) examined the effect on pulmonary function of exposure to 0.4 ppm SO_2 for two hours in healthy male subjects. They observed no changes in FEV_1 (Study ID ◆ 051, 049).

Burton et al. (1969) observed no significant changes in pulmonary function parameters after exposure to 1.1 to 3.6 ppm for 30 minutes in healthy adults (Study ID ◆ 113). Folinsbee et

al. (1985) observed no pulmonary function effects after exposing healthy adults to 1 ppm SO_2 for 2 hours during which time the subjects exercised for three 30-minute periods (Study ID ◆ 122).

Healthy adults were exposed to 2 ppm SO_2 for 30 minutes via free breathing or forced oral or nasal breathing with continuous moderate exercise (Bedi and Horvath, 1989). Pulmonary function was measured before and after exposure. No changes in pulmonary function were observed by any of the three breathing methods (Study ID ◆ 266).

Kulle et al. (1984) exposed healthy adults to 1 ppm SO_2 for four hours per day, three days per week for three weeks. They observed no changes in pulmonary function or bronchial reactivity (Study ID ◆040).

In an effort to standardize procedures for human SO_2 exposure tests, Sandstrom et al. (1988) exposed healthy adults to SO_2 concentrations from 0.4 to 4 ppm for 20 minutes. They observed no changes in pulmonary function parameters as a result of SO_2 exposure (Study ID ● 087).

Lawther (1955) exposed healthy male adults to concentrations of 0, 5, 10, and 20 ppm for 10 minutes each by nose and mouth. No significant consistent changes in respiration were observed in the groups of volunteers. There is limited information on the experimental methods and the reporting of the results is lacking in detail (Study ID ●325).

No effect healthy subjects; effect asthmatics

Several research groups subjected both asthmatic and healthy subjects to the same SO_2 exposure. Some of these studies reported respiratory effects in asthmatics but not in normal subjects.

Jaeger et al. (1979) exposed normal and asthmatic subjects to 0.5 ppm SO_2 for 3 hours and measured pulmonary function parameters. They found no effects from the exposure in the normal subjects; however, they did observe a small decrease in mid-maximal expiratory flow in asthmatics (Study ID ▲ 073).

Schachter et al. (1984) exposed ten asthmatic and ten healthy subjects to 0, 0.25,0.50, 0.75, and 1.0 ppm SO_2 for 40 minutes during exercise. No changes in pulmonary function were observed in the healthy subjects at all concentrations or in asthmatics at concentrations below 1.0 ppm. At 1.0 ppm significant changes in SRaw, FEV_1, and max flow at 50% of vital capacity were observed in the asthmatics (Study ID ◆306).

Linn et al. (1987) exposed 24 normal, 21 atopic, 16 minimal or mildly asthmatic, and 24 moderate or severe asthmatics to 0, 0.2, 0.4, and 0.6 ppm SO_2 for one hour including three 10-minute exercise periods. All the normal and most atopic subjects showed little response at all SO_2 levels. The moderate to severe asthmatics showed the most unfavorable overall responses. In both asthmatic groups, there was a general trend towards increasing response with increased dose. However, responsiveness was variable among individuals and could not be predicted by clinical status (Study ID ◆ 309).

Tan et al. (1982) exposed normal and asthmatic adults to concentrations from 2.5 to 20 ppm SO_2 for 5 minutes. Pulmonary function effects, measured as decreases in specific airway conductance, were observed in both groups, but were significant only in the asthmatic group (Study ID ● 092).

Harries et al. (1981) observed no effect in FEV_1 in non-asthmatics exposed to concentrations of SO_2 up to 15 ppm.

However, asthmatic subjects exhibited decreased FEV_1 at concentrations between 5 and 11.5 ppm. Exposure duration was not clear in the study report (Study ID ● 108).

Effects observed-asthmatic subjects

Gong et al. (1995) investigated the hypothesis that SO_2 induces asthma more than other everyday respiratory stressors. They exposed adult asthmatics to concentrations between 0, 0.5, and 1 ppm SO_2 for 10 minutes, measuring various pulmonary function parameters. They observed adverse changes in pulmonary function at 1 ppm. Exercise exacerbated the effect of SO_2 (Study ID ▲ 077).

Roger et al. (1985) exposed adult asthmatics to 0, 0.25, 0.5, and 1 ppm SO_2 for 75-minute periods during which the subjects did three 10-minute periods of moderate exercise. They observed a dose-dependent increase in specific airway resistance at the 0.5 and 1 ppm levels; however, no effects were observed at 0.25 ppm. They also observed that increases in specific airway resistance after the second and third exercise periods were significantly less than after the first exercise period (Study ID ▲ 081).

Jorres and Magnussen (1990) exposed asthmatic adults to concentrations of 0.5 ppm for 30 minutes of tidal breathing followed by 0.75 ppm during hyperventilation. They observed a small but significant change in SRaw after the exposure (Study ID ▲ 109).

Trenga et al. (1999) found a very diverse response to SO_2 exposure at 0.5 ppm for 10 minutes in adult subjects with mild to moderate asthma. Just over half of the subjects experienced a decrease in FEV_1 and changes in peak expiratory flow (Study ID ◆ 055).

Balmes et al. (1987) investigated the relationship between duration or concentration of exposure to SO_2 and bronchoconstriction in asthmatics. They exposed asthmatics to 0.5 or 1 ppm SO_2 for 1, 3, and 5 minutes through a mouthpiece during eucapnic hyperpnea. They observed small increases in specific airway resistance at both concentrations for 1 minute of exposure. Most subjects developed wheezing, chest tightness or dyspnea after inhalation of 0.5 ppm for both 3 and 5 minutes and 1 ppm for 3 minutes (Study ID ◆ 064).

Tunnicliffe et al. (2001) exposed asthmatic and healthy adults to 200 ppb SO_2 for 1 hour. They observed a small, significant increase in mean respiratory frequency in the asthmatics. Other respiratory measures did not differ between the two groups (Study ID ◆ 071).

Sheppard et al. (1980) investigated whether subjects with mild asthma or seasonal rhinitis have a greater bronchomotor response to SO_2 than normal subjects during mouth breathing. They exposed adult volunteers to 1, 3, and 5 ppm SO_2 for 10 minutes each. Increases in SRaw occurred at lower concentrations in mild asthmatics (4 of 7 asthmatics and 0 of 7 normals at 1 ppm). At 5 ppm all of the asthmatics and 5 of 7 normals exhibited significant increases in SRaw (Study ID ◆375).

Tam et al. (1988) investigated whether bronchomotor responsiveness to SO_2 exposure is related to increased nasal responsiveness. Subjects with asthma or chronic rhinitis were exposed to 2 ppm SO_2 for 4 minutes or 4 ppm SO_2 for 10 minutes (Tam et al., 1988). Significant changes were observed in SRaw and

lower airway symptoms after breathing SO_2 compared to breathing room air. Significant changes in nasal symptoms or nasal resistance were not observed (Study ID ◆ 062).

Kehrl et al. (1987) exposed adult asthmatic subjects to 1 ppm SO_2 to test the effect of exercise and SO_2 exposure. They observed an attenuated response to repetitive exercise, measured by increases in specific airway resistance during three 10-minute exercise periods separated by 15-minute rest intervals. They also observed that pulmonary function effects occur rapidly and are maintained during a 30-minute continuous exercise period (Study ID ◆ 078).

In an investigation of the effects of SO_2 exposure on total respiratory resistance and forced expiratory volume, McManus et al. (1989) exposed asthmatic adults to 0.5 or 1 ppm SO_2 for 20 minutes at rest followed by 10 minutes of moderate exercise. They observed a statistically significant dose-response effect on FEV_1, specific total respiratory resistance, $V_{max\ 50}$ and $V_{max\ 75}$ (Study ID ◆ 098).

Heath et al. (1994) investigated a difference in ethnic susceptibility in asthmatic pulmonary function response when exposed to SO_2 at 1 ppm for 10 minutes at rest and 10 minutes exercising. They observed no ethnic difference, although both groups showed significant decreases in V_{max50}, R_T and FEV_1 compared to pre-exposure values (Study ID ◆ 110).

Bethel et al. (1985) exposed adult asthmatics to 0.25 ppm SO_2 for 5 minutes at rest and 5 minutes during either moderate or heavy exercise. They observed an increase in SRaw during exercise both with and without SO_2 exposure. However, the increase was slightly, but significantly greater with SO_2 exposure than with filtered air (Study ID ◆ 118). Horstman et al. (1986) exposed 27 adults with mild asthma to 0.25, 0.5, 1.0 and 2.0 ppm SO_2 for 10 minutes during moderate exercise with natural breathing. Substantial variability was observed in bronchial sensitivity to SO_2. The concentration of SO_2 which provoked an increase in SRaw 100% greater than the response to clean air ranged between 1.28 and 1.90 for 23 of the subjects, while for the remaining subjects it was greater than 2.00 ppm (Study ID ◆ 303).

Linn et al. (1983a) exposed adult asthmatics to 0.75 ppm SO_2 for 10 minutes during heavy exercise in a chamber, once with unencumbered breathing and once with nose clips and mouthpieces. Greater increases in SRaw were observed upon exposure to SO_2 than with clean air exposure, with the excess increase significantly greater with mouthpiece than with unencumbered breathing (Study ID ◆ 304).

In another study, Linn et al. (1983b) exposed 23 asthmatic adults to 0, 0.2, 0.4, and 0.6 ppm SO_2 for 5 minutes during heavy exercise. There seemed to be a dose-response effect with only the changes at 0.6 ppm being highly significant. The effects seemed to reverse in less than 1 day (Study ID◆ 310).

Horstman et al. (1988) conducted an investigation of the shortest duration of time required to induce bronchoconstriction in adult asthmatics with 1.0 ppm SO_2 during mild exercise. The concluded that significant increases in bronchoconstriction occurred at 2.0 minutes of exposure (Study ID ◆ 311).

Bethel et al. (1983) exposed 9 asthmatic adults to 0.5 ppm SO_2 for 5 minutes while engaging in light, moderate and

heavy exercise. Bronchoconstriction was observed during moderate and to a greater degree with heavy exercise when the volunteers breathed through a mouthpiece. Bronchoconstriction was only observed during heavy exercise when the volunteers breathed through a facemask. Results were variable among volunteers (Study ID ◆ 326).

Sheppard et al. (1981b) investigated whether moderate exercise modifies the bronchoconstriction produced by SO_2 in mild asthmatics. They exposed asthmatics to 0.10, 0.25, 0.50, and 1 ppm of SO_2 through a mouthpiece for 5 or 10 minutes during moderate exercise. Significant bronchoconstriction response was observed for most of the group at 0.25 ppm. The two most responsive volunteers responded at 0.10 ppm. The investigators question whether these responses would occur with oronasal breathing (Study ID ◆ 376).

Wolff et al. (1984) subjected steelworkers with respiratory difficulties to controlled SO_2 exposures at 5 ppm for 2.5 hours. They observed a significant increase in bronchial reactivity after SO_2 exposure. However, changes in actual pulmonary function were seen in only two of the nine subjects (Study ID ● 084).

Fine et al. (1987) observed an increase in SRaw in asthmatics after eucapnic hyperpnea of SO_2 at concentrations up to 8 ppm for one minute (Study ID ● 116).

Linn et al. (1984c) exposed asthmatic adults to 0.6 ppm SO_2 for 6-hour periods on two successive days. The volunteers exercised heavily for 5 minutes at the beginning of the exposures and after 5 hours of exposure. Substantial bronchoconstrictive responses were observed only immediately after exercise. These responses were moderately less severe on the second day of exposure compared to the first (Study ID ● 316).

No effect observed-asthmatic subjects

Bailey et al. (1982) exposed asthmatic subjects to 0, 0.25, and 0.5 ppm SO_2 for one hour by mouthpiece, alternating rest periods with 10-minute periods of moderate exercise. They observed no significant effects in pulmonary function parameters (Study ID ▲ 075). Devalia et al. (1994) exposed asthmatic subjects to 200 ppb SO_2 for 6 hours and measured pulmonary function parameters. They found no significant effects from exposure to SO_2 alone (Study ID ◆ 067).

Linn et al. (1985a) exposed subjects with chronic obstructive pulmonary disease to SO_2 at concentrations up to 0.8 ppm for one hour. They observed no effect on pulmonary function from this exposure (Study ID ◆ 307).

Investigations of effect and recovery

Various studies observed a recovery from symptoms either during or after exposure and after a significant effect on pulmonary function.

Sheppard et al. (1983) investigated whether bronchoconstriction patterns induced by low-level exposures to SO_2 would change upon repeated exposure. They exposed seven non-smoking asthmatics to 0.5 ppm SO_2 for 3 minutes of voluntary eucapnic hyperpnea three times at 30-minute intervals. Seven days later, the same subjects were given only one three-minute exposure. There was a significantly greater increase in specific airway resistance in the first exposure than the second or third exposures. After seven days, specific airway resistance increased as much as it had after the very first SO_2 exposure. The researchers concluded that repeated low-level

exposures can induce temporary bronchomotor tolerance to SO_2 in asthmatic subjects (Study ID ◆ 061). Hackney et al. (1984) investigated the reversibility of bronchomotor effects from SO_2 exposure. Adult asthmatics were exposed to 0.75 ppm SO_2 for three hours, during which the subjects exercised vigorously for the first 10 minutes and rested for the balance of the exposure time. Specific airway resistance was significantly increased after exercise. However, these changes were no longer significant after one hour of exposure. These increases did not persist longer than two hours in the majority of the subjects (Study ID ◆ 079).

Linn et al. (1998) exposed adult asthmatics to 0, 0.3 and 0.6 ppm SO_2 for 10 minutes during heavy exercise. Exercise-induced bronchospasm was observed with no SO_2 exposure. However, bronchoconstriction increased as SO_2 exposure concentration increased. By 30 minutes post-exposure, the lung function of most subjects had returned to pre-exposure levels (Study ID ◆ 097).

Gokemeijer et al. (1973) exposed adults with chronic non-specific lung disease to 10 ppm SO_2 for 3 minutes and observed a marked bronchial obstruction at the end of exposure that decreased to pre-exposure levels 45-60 minutes post-exposure (Study ID ◆ 260).

Toyama and Nakamura (1964) examined changes in pulmonary airway resistance after inhalation of SO_2 at concentrations of 1 to 60 ppm for five minutes in healthy male adults. They observed an increase in pulmonary airway resistance during exposure at all levels, which disappeared several minutes into the exposure. By 15 to 20 minutes post-exposure, airway resistance had returned to control values (Study ID ● 053).

Nose vs. mouth exposure

Several research groups investigated differences in effect as a result of nasal *vs.* oral inhalation. Nasal breathing seems to be more relevant during normal breathing in the absence of physical activity whereas mouth breathing is more relevant during periods of exercise. Speizer and Frank (1966b) exposed healthy male subjects to 15 or 28 ppm SO_2 by inhalation either through the nose or the mouth for 10 minutes. They observed increases in pulmonary flow resistance from both nasal and oral exposure. However, there were more and greater responses from oral than nasal inhalation. There was also greater response from exposure to the higher concentration, on average (Study ID ◆ 054). Kirkpatrick et al. (1982) investigated the effect of breathing route on the bronchomotor response of asthmatics to SO_2 exposure. Asthmatic adults were exposed to humidified air with 0.5 ppm SO_2 for 5 minutes during light to moderate exercise either by mouthpiece (oral breathing), by facemask (oronasal breathing) or by facemask with mouth occluded (nasal breathing). SRaw was increased with all exposure routes. There was no difference in SRaw increases between the oronasal exposure and the oral exposure. However, there was significantly greater increase in SRaw with these two exposure methods than with the nasal exposure. They concluded that nasal breathing seems to provide some protection against SO_2-induced bronchoconstriction in asthmatics exposed to low concentrations of SO_2 (Study ID ◆ 074).

Melville (1970) exposed healthy adults to concentrations of SO_2 between 2.5 and 10 ppm for 10 minutes to an hour by both oral and nasal exposure routes. A statistically significant decrease in specific airway conductance was observed with both exposure routes; however, the effect was greater with oral exposure than with nasal exposure (Study ID ◆ 105).

Bedi and Horvath (1989) observed no significant differences in ventilatory parameters between free-breathing exposure to 2 ppm SO_2 or filtered air in healthy subjects for 30 minutes. However, they did observe significant difference between the free-breathing and the forced oral SO_2 exposure (Study ID ◆ 266).

Effects of temperature and humidity

Sheppard et al. (1984) examined the combined effect of dry (cold) air and SO_2 inhalation on pulmonary function in asthmatic adults. They observed bronchoconstriction at significantly lower SO_2 concentrations when the SO_2 was inhaled in dry cold or warm air rather than humidified warm air. Bronchoconstriction was observed with concentrations in dry air as low as 0.1 ppm for 3 minutes (Study ID ◆ 057).

Bethel et al. (1984) investigated the interaction of cold dry air and SO_2 on asthmatic subjects. Asthmatic and healthy adults were exposure to 0.5 ppm SO_2 in humidified room-temperature air and cold dry air for 3 minutes each. No effects were observed with the humidified room-temperature air with SO_2 for either set of subjects; however, there was an increase in SRaw with exposure to the cold dry air with SO_2 in the asthmatic subjects but not the healthy subjects (Study ID ◆ 123).

Linn et al. (1984a) exposed 24 adult asthmatics to 0, 0.3, and 0.6 ppm SO_2 for 5 minutes at each of three temperatures: 21°C, 7°C, and –6°C with constant relative humidity of approximately 80%. While there was considerable variability between the subjects, cold seemed to exacerbate the overall response to SO_2. The combined stresses acted additively at most, but not synergistically (Study ID ◆ 314).

In a similar study, Linn et al. (1984b) exposed 8 adult asthmatics to 0, 0.2, 0.4, and 0.4 ppm SO_2 for 5 minutes during heavy exercise with both high (85%) and low (50%) relative humidity. Bronchoconstriction increased with increasing SO_2 concentrations, but did not vary significantly with humidity. However, these results should be interpreted with caution, given the small sample size and limitations in experimental design. In another experiment in the same study, 24 adult asthmatics were exposed to 0.6 ppm SO_2 at 5°C and 22°C at high relative humidity. No significant changes in response were observed between the two temperature conditions (Study ID ●313).

Further investigating the effects of temperature and humidity on SO_2 reactivity in asthmatics, Linn et al. (1985a) exposed 22 adult asthmatics to 0.6 ppm SO_2 for 5 minutes during heavy exercise at temperatures of 21°C and 38°C and a relative humidity of 20% and 80%. Greater effects on SRaw were observed at low temperature and low humidity (Study ID ◆ 307).

Non-clinical studies

Effects observed-bronchial clearance

Ferin and Leach (1973) investigated the effect of SO_2 on the clearance of inert particles (TiO_2) from rat lungs. At

exposure to 1 ppm for 170 hours, a slight but statistically significant change in lung clearance was observed. Shorter exposures to 20 ppm also resulted in a statistically significant decrease in clearance (Study ID ◆ 235).
In investigating the effect of SO_2 exposure on early and late clearance of inhaled soluble tracer particles, Mannix et al. (1983) exposed rats to 20 ppm SO_2 for 4 hours. Early clearance (upper respiratory tract) was significantly delayed as a result of SO_2 exposure compared to controls, while late clearance (deep-lung) rates were not significantly different from controls (Study ID ◆ 256).

Oomichi and Kita (1974) investigated the effect of SO_2 exposure on ciliary clearance in excised guinea pig tracheae. A dose-dependent decrease in ciliary activity was observed at exposure to 15, 32, 58, and 77 ppm for 2 to 6 minutes (Study ID ◆ 213).
Riechelmann et al. (1995) examined changes in mucociliary activity in guinea pig trachea with exposure to SO_2 concentrations of 3, 6, 9, 11, and 14 ppm for 30 minutes. They observed a dose-dependent reduction in mucociliary activity (Study ID ● 132).
Knorst et al. (1994) also investigated the effect of SO_2 exposure on mucociliary activity and ciliary beat frequency on guinea pig tracheas. They exposed tracheal samples to 2.5, 5, 7.5, 10, and 12.5 ppm SO_2 for 30 minutes and observed a statistically significant decrease in mucociliary activity at 2.5 ppm. A dose-dependent decrease in ciliary beat frequency was observed at SO_2 concentrations higher than 5 ppm, in addition to further reductions in mucociliary activity at higher SO_2 concentrations (Study ID ● 164).

Trimpe et al. (1986) investigated the effect of SO_2 on the clearance of *Listeria monocytogenes* from normal and emphysematous hamster lungs. After exposure to 27±3 ppm SO_2 for 35 days, a decrease in the number of *L. monocytogenes* recovered from both normal and emphysematous hamsters was observed (Study ID ● 134).

A number of studies investigated the nasal mucociliary transport rates in chickens after exposure to various SO_2 concentrations and durations of exposure. Wakabayashi et al. (1977) exposed chickens to SO_2 intermittently for 16 hours a day for 7 days at concentrations of 1.4 to 66 ppm. The mucociliary transport in the nasal mucus membranes was observed. Peaks of increased intranasal transport time with intervening recovery periods were observed at all concentrations. Transport in the sinus was decreased at concentrations above 10 ppm (Study ID ● 129).
Ukai et al. (1984) also investigated mucociliary function in chickens. After exposure to concentrations between 18 and 40 ppm, a deceleration of turbinate clearance was observed, as was a decrease in sinus clearance rates (Study ID ● 137). A previous study (Ukai et al., 1983) found similar decreases in turbinate clearance in chickens for both continuous and intermittent SO_2 exposure for 1 hour, 4 times/day for 2 days at concentrations between 4 and 40 ppm (Study ID ● 138). Majima et al. (1985) also observed decreases in mucociliary transport rate in chickens exposed to 6 ppm SO_2 16 hours a day for 7 days (Study ID ● 149).

Effects observed-bronchoconstriction or specific airway resistance

Chickens

No effects on tidal volume or respiratory frequency were observed in chickens exposed to 100 ppm SO_2 breathing through their nostrils and mouth, but a small, statistically significant increase in minute volume was observed (Fedde and Kuhlman, 1978). At 500 ppm SRaw decreased; at 1000 ppm SRaw initially decreased, then subsequently increased. Also at 1000 ppm, respiratory frequency and minute volume decreased. The effects seen at 1000 ppm were increased at 5000 ppm. All exposures lasted 60 minutes (Study ID ▲ 183).

Rabbits

Barthelmy et al. (1988) investigated cold-induced bronchospasm in rabbits exposed to 0.5 or 5.0 ppm SO_2 for 45 minutes. Dose-dependent increases in lung resistance were observed, returning to control values by 40 minutes post-exposure. However, cold-induced bronchoconstriction was decreased by prior exposure to SO_2, suggesting a protective effect on SO_2 exposure and cold-induced bronchomotor response (Study ID ▲ 197).

Davies et al. (1978b) exposed rabbits to either 300 ppm for three hours or 150 ppm for 12 three-hour periods. They observed higher lung resistance in animals exposed to 300 ppm, three days after exposure, but no differences in those animals exposed to 150 ppm. In addition, both groups of animals exhibited decreased breathing frequency, but recovery times were faster for those animals exposed to 300 ppm for three hours (Study ID ◆ 239).

Davenport et al. (1984) exposed rabbits to 200 to 400 ppm SO_2 for 15 to 20 minutes. They observed decreased breathing frequency and increased tidal volume in the exposed animals compared to controls (Study ID ◆ 244).

Citterio et al. (1985b) exposed rabbits to 300 to 350 ppm for an unreported total exposure time. Statistically significant increases in inspiratory and expiratory time were observed as well as a rising rate of diaphragm activity. The effects were observed for up to 30 minutes post-exposure (Study ID ● 194).

Davies et al. (1978a) observed decreased Breuer-Hering reflex and activity in 23 of 26 stretch receptors as well as increased inspiratory time and decreased expiratory time in rabbits exposed to 200 ppm SO_2 for 10-minute periods (Study ID ● 234).

Guinea pigs

Park et al. (2001) investigated enhanced pause as an index of airway obstruction as a result of SO_2 exposure. Guinea pigs were exposed to 0.1 ppm SO_2 for five hours a day for five days. Significant increases in respiratory pause were observed after SO_2 exposure (Study ID ▲ 259).

Guinea pigs exposed to levels of 50 to 500 ppm SO_2 for 15 minutes exhibited reductions in dynamic compliance and conductance (Atzori et al., 1992). No effects were seen at lower concentrations; however, pretreatment with 10 ppm provided a protective effect against bronchoconstriction upon subsequent exposure to 250 ppm SO_2 (Study ID ◆ 189).

Amdur et al. (1983) investigated the effect SO_2 and ZnO alone and in combination on the respiratory mechanics of guinea pigs. 1 ppm SO_2 for one hour resulted in an increase in respiratory resistance and a decrease in respiratory compliance, both statistically

significant. Mixtures of ZnO and SO_2 resulted in changes in lung function relative to control animals that were not always significantly different from SO_2 exposure alone (Study ID ◆ 229).
Halinen et al. (2000a) exposed guinea pigs to SO_2 in cold dry air for four consecutive 10-minute periods at concentrations of 0, 1, 2.5, and 5 ppm. A dose-dependent increase in bronchoconstriction was observed at 1 and 2.5 ppm compared to the initial exposure to clean dry air. In the fourth exposure period, which involved concentrations of 5 ppm, a smaller bronchoconstriction response was observed (Study ID ◆ 245). In a follow-up study, guinea pigs were exposed to 1 ppm SO_2 in cold dry air for one hour continuously (Halinen et al., 2000b). Weaker effects on lower respiratory function were observed in this study than in the first study (Study ID ◆ 246).
Amdur (1959) exposed guinea pigs to SO_2 concentrations between 2 and 1000 ppm. A dose-dependent increase in bronchial constriction was observed after a one-hour exposure at these levels. Bronchoconstriction was increased for the duration of a three-hour exposure to 24 ppm, with lung function returning to baseline values within three hours post-exposure. Bronchial constriction was greater when animals were exposed through tracheal cannulae rather than respiring normally (Study ID ● 216).
Amdur and Underhill (1970) exposed guinea pigs to SO_2 and Fe_2O_3 or open-hearth dust, singly and in combination, to determine any interaction effects. They observed significantly increased levels of airway resistance upon exposure to SO_2 levels from 1.5 to 26 ppm for one and two hours. The combination of pollutants did not result in significantly different levels of respiratory response from SO_2 exposure alone (Study ID ● 227).

Mice

Sensory irritation, as measured by decreased respiratory rate, was investigated in mice exposed to SO_2 (Alarie et al., 1973). Single exposures to 17, 32, 62, 89, 123, 198, and 298 ppm for 10 minutes decreased respiratory rate significantly compared to no exposure. A dose-dependent relationship was observed between rapidity of onset and depth of respiratory depression, and SO_2 exposure (Study ID ◆ 243).
Leong and MacFarland (1965) exposed rats to SO_2 concentrations of 40, 64, 83, 145, 231, 426, and 751 ppm for two hours to observe indications of respiratory stress. They found a dose-dependent decrease in percent SO_2 retention, respiratory rate, and minute volume as SO_2 concentration increased (Study ID ◆ 253).

Dogs

Cho et al. (1968) exposed anaesthetized dogs to 11 to 1000 ppm SO_2 for 0.1 to 6 minutes. Exposure at all levels initiated bronchoconstriction in all the dogs tested (Study ID ● 167).
Frank et al. (1965) exposed mongrel dogs to SO_2 concentrations ranging between 7 and 230 ppm for 15 to 20 minutes. Exposures were by nose, by tracheal cannula, and by an isolated segment of trachea. Exposure by nose resulted in an observed increased in nasal flow resistance (Rn), roughly proportional to SO_2 concentration. Rn reverted partially or totally to control levels within 15 to 40 minutes post-exposure. Pulmonary flow resistance (Rl) followed the same pattern, with smaller effects observed, and an increase in Rl during recovery. The greatest

change in Rl was observed with tracheal cannula exposure. A lesser increase in Rl was observed with isolated tracheal exposure (Study ID ● 170).

Lewis and Kirchner (1984) exposed dogs to 10 and 30 ppm SO_2 for 5 minutes. Pulmonary resistance and compliance did not change at 10 ppm. However, increased lung hypersensitivity to aerosolized methacholine occurred after exposure to 30 ppm and was maximal at four hours post-exposure (Study ID ● 258).

Eady and Jackson (1989) exposed dogs to 400 ppm SO_2 for 2 hours. They observed an immediate increase in bronchial response to histamine. This response returned to normal levels by 2 hours after exposure. However, 24 hours after exposure a second phase of bronchial responsiveness occurred which lasted for several days (Study ID ● 190).

Islam et al. (1972) exposed dogs to 0, 1, 2, 5, and 10 ppm SO_2 for three 60-minute periods and observed increased bronchial sensitivity to acetylcholine compared to controls. Maximum sensitization was observed at 2 ppm SO_2 (Study ID ● 162).

Norris and Jackson (1989) reported airway hyperreactivity to histamine in dogs exposed to 200 ppm SO_2 for 2 hours (Study ID ● 146).

Frank and Speizer (1965) exposed dogs to concentrations of 7-16 ppm, 25-34 ppm, or 60-61 ppm SO_2 for 20 minutes by nose, tracheal cannula, or by an isolated segment of the trachea. Nasal flow resistance increased in a roughly dose-dependent manner during nasal exposure. Recovery took between 15 and 40 minutes. Little change was observed in pulmonary flow resistance. During exposure by tracheal cannula, pulmonary flow resistance increased quickly to a peak, after which it receded. The isolated tracheal exposure produced less pronounced changes in pulmonary flow resistance. All of the observed effects were variable (Study ID ● 170).

Cats

Grunstein et al. (1977) exposed cats to 3000 to 7000 ppm SO_2 for 24 to 40 seconds. They observed a reduction in tidal volume, and increased respiratory frequency and pulmonary resistance (Study ID ● 186).

Corn et al. (1972) exposed 20 healthy male cats to 15-25 or 30-40 ppm SO_2 for 30 minutes and observed alterations in pulmonary flow resistance. No animals responded at concentrations lower than 20 ppm and only one animal showed a significant increase in pulmonary flow resistance at this level. Results were variable between the cats. There are inconsistencies in the reporting and limited detail in the experimental methods and results sections of the paper (Study ID ●290).

Thompson et al. (1990) exposed cats to 100, 500, 800, and 1000 ppm SO_2 for 1, 5, and 10 breaths. A concentration dependent response was observed in lung resistance with the administration of 10 breaths of 100 to 1000 ppm SO_2. The results were variable among the subjects. Limited information on the experimental design and the results is provided. The study design did not appear to follow Good Laboratory Practice guidelines (Study ID ●372).

Sheep

Allergic and normal sheep were exposed to 5 ppm SO_2 for 4 hours to investigate airway reactivity (Abraham et al., 1981). No differences from control values were observed in either normal or allergic sheep directly after exposure. 24-hours after exposure, airway reactivity in the

allergic sheep increased significantly (Study ID ◆ 230).
A similar study exposed normal and allergic sheep to SO_2 for 4 hours (Abraham et al., 1980). In this study normal sheep were divided into two groups based on SO_2 exposure concentrations: 5 and 10 ppm. The allergic sheep were exposed to only 5 ppm. Airway reactivity was not significantly changed directly after exposure; however, both the normal sheep exposed to 10 ppm SO_2 and the allergic sheep exhibited increased airway reactivity 24-hours post exposure (Study ID ◆ 231).

Donkeys
Spiegelman et al. (1968) exposed miniature donkeys to SO_2 levels ranging from 27 to 713 ppm for 30 minutes to observe any effects on bronchial clearance of radioactive monodisperse ferric oxide particles. No effect on bronchial clearance was observed at concentrations below 300 ppm. Higher concentrations produced severe cough and slowing or transient arrest of bronchial clearance (Study ID ● 205).

Effects observed-other
Giddens and Fairchild (1972) exposed mice to 10 ppm SO_2 for 4 to 72 hours to observe the effect of SO_2 exposure on the nasal and respiratory tracts. Lesions consisting of edema, necrosis, and desquamation of the olfactory and respiratory epithelium were observed at 24-hour and longer exposures. More injury was observed in the nasomaxillary turbinates than in the rest of the respiratory tract (Study ID ◆ 191).
Ukai (1977) investigated the effect of SO_2 exposure (0.03 to 0.1 ppm for 4 weeks) on upper respiratory infection response in mice inoculated with influenza virus. More rapid and more severe inflammatory response, as well as more rapid development and higher levels of HI titer were observed in the SO_2-exposed mice (Study ID ◆ 207).
Fairchild (1977) observed an inhibition in the growth of influenza virus in the noses of mice exposed to 6 ppm of SO_2 for 7 days. Virus propagation was not altered (Study ID ◆ 238).
Hanacek (1987) investigated the effect of SO_2 on cough and expiratory reflexes of 22 anaesthetized rabbits. Exposure to 200-300 ppm SO_2 for 10-15 minutes resulted in decreases in both mechanically stimulated cough excitability and cough reflex strength in rabbits. Reporting of the experimental methods and results lack detail (Study ID ●300).

No effects observed
Exposure of guinea pigs to 0.2, 0.4, and 0.8 ppm SO_2 for 2 hours produced no statistically significant changes in respiration (Amdur et al., 1978; Study ID ◆ 204).
Guinea pigs were exposed to 1 ppm SO_2 for two 60-minute exposures at high and low relative humidities (McJilton et al., 1976). No significant change was observed in pulmonary flow resistance with SO_2 exposure at either high or low relative humidity. The objective of the study was to measure the interaction of SO_2 and sodium chloride aerosol. Significant changes in pulmonary function were observed only when the two inhalants were administered together at high relative humidity (Study ID ◆ 257).
Amdur and Underhill (1968) investigated the respiratory response of various soluble and insoluble aerosols, including SO_2, in guinea pigs. No statistically significant changes in

pulmonary flow resistance were observed after exposure to 2 ppm SO_2 for 10 minutes (Study ID ● 226).
Donkeys were exposed to SO_2 concentrations between 53 and 300 ppm for 30 minutes to investigate the effect of SO_2 exposure on mucus transport rates and the clearance of gamma-tagged insoluble aerosols (Lippman et al., 1975). No changes in mean residence time of the aerosols in the respiratory system were observed at any SO_2 concentrations (Study ID ● 263).
Hanacek et al. (1991) observed the cough reflex elicitability (CRE); cough reflex strength (CRS), and Hering-Breuer inflation index (HBIR) in rabbits 24- and 48-hours after exposure to 200 to 300 ppm SO_2 for 10 to 20 minutes. Some changes were observed in the exposed animals but none were significantly different from controls (Study ID ● 161).

Epidemiology studies

Children

Boezen et al. (1999) conducted a study investigating whether children with bronchial hyperresponsiveness and high serum concentrations of total IgE are susceptible to air pollution. They observed a significant increase in the prevalence of lower respiratory symptoms in children with bronchial hyperreactivity and high serum IgE concentrations with 15 ppb incremental increases in ambient air pollution (24 hr mean: 3.2-8.6 ppb). The ORs ranged from 1.28 to 2.49 (95% CI range 1.00-4.04) for lag days 0,1, and 2 and a 5-day mean (Study ID ◆ 005).
Dockery et al. (1982) measured the pulmonary function of children in Steubenville, Ohio, before and immediately after air pollution alerts with SO_2 concentrations between 64 and 174 ppb at various times over a two-year period. Pulmonary function was also measured weekly for three weeks after the alerts. Pulmonary function and SO concentration were analyzed by regression. There was a slight but statistically significant decrease in pulmonary function with increasing SO_2 concentrations (Study ID ◆ 013).
Hoek and Brunekreef (1993) investigated the effect of winter air pollution episodes on the respiratory health of children. Spirometry tests were performed and ambient air concentrations of SO_2, black smoke, PM_{10}, and NO_2 were measured. During an air pollution episode with daily average SO_2 concentrations above 38 ppb, FVC, FEV_1 and MMFR were lower than baseline values. No association was observed between other pollutants and lung function test results (Study ID ◆ 018).
Schwartz et al. (1994) investigated ambient air pollution exposures and respiratory illness in elementary school children in 6 US cities. SO_2 was not significantly associated with cough incidence or upper respiratory symptoms. SO_2 seemed to be significantly associated with lower respiratory symptoms (OR 1.28; (5% CI 1.13-1.46) with 10 ppb incremental increases from an ambient concentration greater than 22 ppb, although this association appeared to be derived from a few influential observations and needs to be interpreted with caution (Study ID ◆ 426).
Segala et al. (1998) found a significant increase in incidence of asthma attack in mild asthmatics with an incremental increase of 19 ppb SO_2 for the same day (OR 2.86, 95%CI 1.31-6.27) and for lag day 1 (OR 2.45; 95%CI 1.01-5.92) while

investigating childhood asthma and air pollution in Paris. SO_2 concentrations ranged from 1.7 to 32 ppb with a mean of 8.3±5.1 ppb (Study ID ◆ 448).
Roemer et al. (1993) investigated air pollution and occurrence of respiratory symptoms in children with chronic respiratory symptoms in The Netherlands. A small but statistically significant association (OR not reported) was observed between SO_2 concentrations and both morning and evening peak flow. Highest 24-hour average and 1-hour maximum were 40 ppb and 56 ppb, respectively (Study ID ◆ 449).
Agocs et al. (1997) conducted a longitudinal study of lung peak expiratory flow rates in asthmatic children and ambient air pollution in Budapest, Hungary. A consistent, significant association between SO_2 exposure (Median: 16 ppb Range: 11-55 ppb) and peak expiratory flow was not observed. A training effect was not considered and accurate information on medication use was not available. Exposure to environmental tobacco smoke was common and not accounted for (Study ID ● 362).
Romieu et al. (1995) observed an association between total number of emergency visits for respiratory disease in children and incremental 19 ppb increases in levels of SO_2 on the same day in Mexico City (mean concentrations: 70 ppb; range: 10-490 ppb). The associations between number of emergency visits for asthma or total number of emergency visits and SO_2 concentration were not statistically significant. Relative risks and confidence intervals were not reported, limited details are available on the exposure assessment, misdiagnosis was possible in the very young children and some results are reported to be significant when they are not (Study ID ● 385).
Lin et al. (2003) observed an association between asthma hospitalization and exposure to SO_2 lagged over 6 or seven days in girls aged six to twelve, but not in boys, in Toronto, Ontario. There was limited information on exposure assessment and monitoring. The bidirectional crossover design of the study makes it difficult to compare to other studies (Study ID ● 394).
Lee et al. (2002) observed a statistically significant association (OR 1.11; 95% CI 1.06-1.17) between hospital admissions for asthma in South Korean children and an incremental 4.4 ppb increase in ambient SO_2 (mean 7.7 ±3.3 ppb). However, there was limited information on exposure monitoring and assessment and the results of some of the models were inconsistent (Study ID ● 398).
Delfino et al. (2003) observed significant associations between bothersome (OR 1.23; 95%CI 1.06-1.41) and more severe (OR 1.36; 95%CI 1.08-1.71) asthma symptoms in Hispanic children in Los Angeles with incremental 3.8 ppb increases in ambient SO_2 (mean 6.5 ppb; range: 1.0-26.1 ppb). However, limitations of this study include small, non-random sample, no validation of peak expiratory flow measurements and asthma symptoms, and inconsistent exposure monitoring (Study ID ● 413).
Chew et al. (1999) report a significant positive correlation (OR 1.80-2.90; 95%CI not reported) between an incremental 7.6 ppb increase in SO_2 levels lagged by 1 or 2 days and daily asthma emergency room visits in children in Singapore in this ecological study (mean concentrations 14.5±8.3 ppb). However, confidence intervals are not reported and there was a substantial

amount of missing SO_2 data (Study ID ●456).

Hajat et al. (1999) reported a statistically significant association (5.8%; 95%CI 1.6%-10.2%)between GP consultations for asthma and other lower respiratory diseases in children and an approximately 6.8 ppb change in ambient levels of SO_2 (mean 8.4±3.4 ppb). No significant findings were reported for adults and the elderly. Confidence intervals were wide and there was limited information on exposure monitoring (Study ID ● 469).

Mortimer et al (2001) observed an association between a 2-day moving average lag increase in SO_2 (range between cities ~ 5 – 75 ppb; average: 53 ppb) and morning asthma symptoms in asthmatic children aged 4 to 9 years in the USA (OR 1.48). Some confounding factors, such as exposure to cigarette smoke were not considered. Confidence intervals were not given (Study ID ● 432).

Garty et al. (1998) observed a but not statistically significant positive correlation between emergency room visits for acute asthma attacks in children and ambient mean SO_2 concentrations (range 11-27 ppb). The authors also estimated that approximately 28% of the variance in the number of ER visits was explained by fluctuations in SO_2. However, statistical significance was not calculated and both outcome and exposure misclassification are possible (Study ID ●485).

Peters et al. (1996) reported a weak association between incremental 51 ppb increases in SO_2 and decreases peak expiratory flow in children in East Germany and the Czech Republic (mean concentrations: 27.1-90 ppb). However, these results were not statistically significant. Exposure assessment was a limitation of this study as was the outcome data collection (Study ID ● 435).

Queiros et al. (1990) observed very small significant correlations (r = 0.334 monthly p=0.01; r=0.473 quarterly p=0.07) between monthly and quarterly mean ambient SO_2 concentrations (9.1±3.1 ppb) and asthmatic attacks on children in the Oporto area of Portugal. Limited details are given on SO_2 concentrations, consideration of confounders, grouping of outcome status groups, and confidence intervals (Study ID ●445).

Braun-Fahrlander et al. (1992) found no statistically significant associations between ambient SO_2 levels (range: 11-27 ppb) and respiratory symptoms in children in two cities in Switzerland. Details of the analysis of the SO_2 data are limited (Study ID ● 450).

Henry et al. (1991) found no significant association between daily ambient SO_2 levels (>10.9 ppb) and asthma symptoms in children in two towns in New South Wales, Australia. Confounders were not addressed and exposure assessment is a limitation of this study (Study ID ● 451).

Keiding et al. (1995) found no association between SO_2 levels (daily averages: 0-38 ppb) and number of total contacts or contacts for respiratory illness with the Copenhagen Emergency Medical Service in children. An influenza epidemic at the beginning of the study may have confounded the results. In addition, monitoring was a limitation due to the placement of the monitors and lack of detail regarding the variations in SO_2 levels among the monitoring stations (Study ID ● 457).

Yu et al. (2000) observed no significant association between incremental 10 ppb

increases in ambient SO_2 concentrations (daily mean: 8.0 ppb) and asthma symptoms in children in Seattle, Washington. Potential confounders such as other outdoor pollutants, meteorological factors, and respiratory infection were not considered and exposure assessment was based on averages of regional monitoring (Study ID ● 462).

Roemer et al. (1998) reported no clear association between SO_2 (daily concentration range: 1.0 – 43.5 ppb) and morning or evening PEF in the Pollution Effects on Asthmatic children in Europe (PEACE) study. Respiratory infections were not considered and may have confounded the analysis. Timing of morning PEF measurements followed a long period of indoor exposure, so exposure assessment using ambient measurements may lead to misclassification (Study ID ● 467).

Hospital admissions or other incidence of chronic obstructive pulmonary disease (COPD)

Dab et al. (1996) examined hospital admissions for respiratory diseases in Paris as part of the APHEA project. 24 hour (mean: 11 ppb) and 1 hour maximum (mean: 23 ppb) SO_2 concentrations were significantly associated with admission for COPD for same-day exposure (Study ID ◆351).

Anderson et al (1997) investigated the short-term effects of air pollution on hospital admissions for COPD in Europe as part of the APHEA project (Air Pollution and Health, a European Approach). The effect of an incremental 19 ppb increase in SO_2 varied considerably across the cities (Amsterdam, Barcelona, Paris, Rotterdam) and was not statistically significant for all ages. In the warm season, borderline significant results (daily OR 1.05 95%CI 1.01-1.10) were observed between hospital admissions for COPD and an incremental 19 ppb increase in daily mean SO_2 levels (17.9-31.3 ppb) with inconsistent lags of either the same day or day 2 (Study ID ◆ 369).

Desqueyroux et al. (2002 a,b) observed no association between physician-monitored exacerbation of COPD symptoms (Study ID ◆ 406) or asthma (Study ID ◆ 402) and mean 24 hr concentrations of SO_2 in Paris. SO_2 concentrations ranged from 0.76 to 10 ppb in the summer (mea: 2.7 ±1.9 ppb) and from 1.1 to 31 ppb in the winter (mean: 7.3±4.6 ppb). ORs were calculated for a 4 ppb increase in SO_2 concentrations.

Tenias et al. (2002) investigated the short-term effects of air pollution on emergency room visits for COPD in Valencia, Spain. An incremental 4 ppb increase of SO_2 was not associated with emergency room visits for COPD (24-hr mean 10.4 ppb; range 2.0-26.1 ppb) (Study ID ◆ 431).

Sunyer et al. (1991) found a small but statistically significant association (0.70/day at 38 ppb $p<0.01$; 0.55/day at 57 ppb $p<0.01$; 0.70/day at 27 ppb $p=0.04$) between daily number of emergency room admissions for chronic obstructive pulmonary disease and daily levels of SO_2 in an ecological study in Barcelona. An incremental increase of 38 ppb daily mean SO_2 levels (24-hr averages: 27, 38, and 57 ppb) led to an average of 2 additional admissions per day. There is some question as to the diagnosis of COPD, suggesting possible misclassification or overestimation of admissions. 20% of the SO_2 monitoring data was unavailable due to

malfunctioning equipment (Study ID ● 439). In a later study, Sunyer et al. (1993) concluded that an incremental 9.5 ppb increase in ambient SO_2 levels (baseline unreported) resulted in a 6% increase in COPD emergency admissions in the winter and 9% in the summer in Barcelona over a 5-year period. Socioeconomic confounders could not be considered because outcome data was obtained from registries rather than personal testing or questionnaires. Mean levels of SO_2 and confidence intervals were not reported in this study (Study ID ● 437).

Wong et al. (1999) reported weakly significant associations (≥65 years OR 1.023 95%CI 1.012-1.036; all ages OR 1.013 95%CI 1.004-1.021) between an incremental increase of 4 ppb in ambient SO_2 levels (mean 6.5 ppb; range 1.0-26.1 ppb) and hospital admissions for respiratory disease and COPD. Information on the exposure monitoring is limited and it is suggested by the study authors that exposure classification is a weakness of the study (Study ID ● 481).

Hospital admissions or clinic visits for respiratory disease and/or asthma

Bates and Sizto (1987) investigated hospital admissions and air pollution data in Southern Ontario for January, February, July and August in 1974 and 1976 to 1983. Mean hourly SO_2 peaks were 2.21 to 5.14 ppb in the winter and 1.65 to 3.97 in the summer. Significant correlations (correlation and confidence intervals not reported) were found between SO_2 and deviations from the mean respiratory admissions for day of the week, season and year. The study authors warn that hospital and emergency room admission data may be unreliable in classifying outcomes (Study ID ◆367).

Walters et al. (1994) looked at hospital admissions for respiratory disease and asthma and ambient levels of SO_2 and smoke in Birmingham, UK. Mean and max levels of SO_2 were 15 ppb and 48 ppb, respectively. Daily SO_2 levels were weakly, but significantly (15.5 admissions 95%CI 6-25), associated with hospital admissions for respiratory diseases for the same day in the summer and with a two-day lag in the winter (Study ID ◆ 340).

Wong et al. (2002) looked at daily air pollution and daily hospital admissions for asthma and other respiratory admissions in Hong Kong and London, England. Asthma admissions were not significantly associated with an incremental 4 ppb increase in SO_2 in either city (mean 6.8±4.7 ppb). The association with respiratory admissions was small, but significant in Hong Kong (associations and confidence intervals not reported) (Study ID ◆ 423).

Emerson (1973) studied 32 volunteers with chronic airways obstruction weekly for up to 82 weeks to assess a relationship between respiratory function and changes in atmospheric conditions and air pollution. SO_2 (mean 73.4±40 ppb) was reported to be significantly correlated (associations and confidence intervals not reported) with FEV_1 in one volunteer and with MEFR in two volunteers. The observational protocol varied considerably among the volunteers and significance was not clearly established (Study ID ●342).

Ponce de Leon et al. (1996) investigated short-term effects of London air pollution (daily SO_2 averages: Daily average: 12±5 ppb on hospital admissions for respiratory disease from 1987 to 1992. Weak and questionably significant associations were reported between an increase in SO_2

concentrations from the 10th to the 90th percentile and two different ages groups and two seasons. The significance of these results is questionable due to the number of significant figures used in the calculation of the RR and the confidence intervals (15-64 year group in the cool season for a 7-19 ppb increase in SO_2: RR = 1.0389, 95% CI 1.0010-1.0783; 0-14y group in the warm season for a 7-16 ppb increase in SO_2 RR=1.0468, 95%CI 1.0066-1.0885) (Study ID ● 346).

Ponka and Virtanen (1996b) observed inconsistencies in their observations of associations between ambient air pollution and hospital admissions for asthma. Positive associations (associations not reported) were observed for 24-hour SO_2 concentrations (means: 5-10 ppb) and asthma admissions. However, significant positive associations (associations not reported) were also observed for digestive tract disease (the control) and the control exposure level. This suggests that the modeling may have been unsatisfactory (Study ID ●347).

Hwang and Chan (2002) observed significant associations between current day SO_2 concentrations and daily numbers of clinic visits for lower respiratory illness in Taiwan. SO_2 concentrations ranged from 1.5 to 16.9 ppb with a mean of 5.4±3.0 ppb. People over 65 seemed to be the most susceptible and the associations decreased as lag day increased. Associations and confidence intervals are not reported and the exposure assessment is a limitation (Study ID ●393).

Martins et al. (2002) reported a significant association (18% increase in visits; range 4.14%-31.85%) between a six-day moving average of SO_2 (4.5 ppb) and emergency room visits for chronic lower respiratory disease in the elderly in this ecological study in Sao Paulo, Brazil. There is limited information on exposure monitoring or on the justification of representative cases (Study ID ● 399).

Jaffe et al. (2003) found inconsistent results in Cincinnati, Cleveland, and Columbus, Ohio when investigating the number of daily emergency department visits and air pollution for asthmatics aged 5 to 34 years. The authors report a 12% increased risk of an emergency department episode (95%CI 1-23%) with a 19 ppb incremental increase in SO_2 across all cities (daily mean 13.7±9.6 ppb; 15.0±9.7 ppb; 4.2±3.2 ppb). However, inconsistencies in the reporting of the results, uncontrolled confounding, and potential exposure misclassification limit confidence in these findings (Study ID ● 409).

Hajat et al. (2002) observed seasonally-dependent significant increases in the number of physician consultations for upper respiratory disease in London, England for adults (4.6% change in admissions 95%CI 1.5-7.7%) and those 14 years and younger (cool season: 5.5 % 95%CI 2.4-8.7%; all year: 3.5% 95%CI 1.4-5.8%) associated within incremental increases of SO_2 between 5.7 ppb and 7.8 ppb (mean warm season: 7.8±2.5; mean cool season: 8.4±3.4). Significant changes were not observed in the elderly. The likelihood of both outcome and exposure misclassification limits confidence in this study (Study ID ●410).

Pinter et al. (1996) report significant correlations (associations not reported) between daily concentrations of SO_2 and incidence of acute respiratory morbidity. Confounding factors such as temperature, concentration of pollution from domestic heating (homes heated by

low-quality coal), and frequency of infection were not considered and SO_2 levels are not clearly reported (Study ID ● 428).

Hoek and Brunekreef (1994) observed small significant positive associations between previous day SO_2 concentrations (mean: 5.7±5.5 ppb) and daily respiratory symptoms (cough OR 1.10; LRD OR: 1.18), but not pulmonary function in the Netherlands. Pulmonary function testing was carried out but all other symptoms were assessed by diary or interview, introducing the possibility of recall and personal bias. Confidence intervals were not reported (Study ID ● 444).

Schwartz (1995) reported that SO_2 levels were significant predictors of hospital admissions for respiratory disease in two cities in the USA with very different ratios of SO_2-to-PM (SO2 concentrations New Haven 29.8 ppb; Tacoma 16.8 ppb). The lag day differed between the two cities. Climate differences between the cities may have confounded the analysis. Control for O_3 substantially weakened the association with SO_2 and relative risks were very low (New Haven RR 1.03 95%CI 1-1.13); Tacoma RR 1.06 95%CI 1.01-1.12) (Study ID ● 471).

Peters et al. (1997) observed a weak, but statistically significant decrease in evening peak expiratory flow (-1.67 range: -2.76 to -0.58) for a 25 ppb incremental increase in 5-day mean levels (mean 27.2 ppb; max 146.2 ppb) of SO_2 in the Czech Republic. Only one monitor was used to measure SO_2 concentrations in this city-wide study. The criteria used to check the validity of PEF measurements was substantially more lenient than other studies (Study ID ● 472).

Other asthma incidence

Using neural networks, Moseholm et al. (1993) investigated function changes in asthmatics and low-level SO_2 and other atmospheric factors. The range of the 24hr means of ambient SO_2 was 6.5 to 6.8 ppb. Over the 8-month period, subjects kept a diary detailing symptoms, lung function, medicine intake and tobacco smoking. Lung function was associated with ambient SO_2 concentrations of SO_2, as well as with temperature, relative humidity, and medicine intake. Increased SO_2 concentrations corresponded to decreased peak flow levels at concentrations above 15 ppb (Study ID ◆ 333).

Buchdahl et al. (1996) reported significant associations (OR 1.12 95%CI 1.06-1.17) between variations in daily SO_2 concentrations (5.3 ppb incremental increase; mean 8.4±5.3 ppb) and the incidence of acute wheezy episodes, after adjustment for season. However, other compounds in air pollution were not considered, and the reliability of the outcome diagnoses was questionable (Study ID ● 364).

Tarlo et al. (2001 assessed possible associations between ambient SO_2 concentrations and symptomatic colds in the production of asthma exacerbations. An association was observed from March to November (no association reported, $p<0.1$) between higher levels of SO_2 (4.94 ppb vs. 3.04 ppb) for 3 days before asthma exacerbation with a cold compared with asthma exacerbations without a cold. Cold diagnosis depended on diary reporting by subjects and there are limitations in exposure assessment (Study ID ●433).

Neukirch et al. (1998) reported significant associations between an incremental 19 ppb increase (mean

8.3±5.2 ppb; range 1.7-32.0 ppb) in SO_2 (5 day lag) and incidence of wheeze (OR 1.35 95%CI 1.10-1.81) and nocturnal cough (OR 1.34 95%CI 1.00-1.79) (lag days 3 and 5) in asthmatics in Paris in the winter. SO_2 levels also correlated significantly with decreased morning peak expiratory flow. Sample size was small: n=40, who were then divided into two groups. Only significant findings were reported. Selection bias may be a factor. Little detail is given on the SO_2 data and monitoring (Study ID ● 455).

Other hospital admissions

Ponka (1991) found significant correlations of daily concentrations of SO_2 (daily mean 7.3±4.8 ppb; range 0.08-36.1 ppb) and admissions to emergency wards in the elderly (7% more admissions during higher pollution; confidence interval not reported). However, cold weather and other pollutants also had effects and SO_2 was highly correlated with these factors (Study ID ● 453).

No associations observed

Kesten et al. (1995) investigated a relationship between emergency room visits for asthma and atmospheric pollutant concentrations. SO_2 concentrations over the yearlong study were measured to be between 0 and 1.5 ppm (0-1500ppb). No association was observed between SO_2 and emergency room visits; however, some association was observed with other air pollutants (Study ID ◆ 023).

Moolgavkar et al. (1997) investigated air pollution and hospital admissions for chronic obstructive pulmonary disease (COPD) in Minneapolis-St. Paul, Minnesota and Birmingham, Alabama from 1986 to 1991. SO_2 analysis was not done in Birmingham due to a large amount of missing information. There were no significant associations between hospital admissions (increase in admissions 1.6% 95%CI -0.1%-3.3%) and 3.5 ppb incremental increase in SO_2 concentrations (mean 4.8-6.6 ppb). The study authors point out that confounding by other pollutants cannot be ruled out. Very little detail is given regarding the exposure monitoring (Study ID ●331).

Schouten et al. (1996) investigated the short-term relationship between air pollution and the daily number of emergency hospital admissions for respiratory disease in Amsterdam and Rotterdam as part of the APHEA project. Results were inconsistent with both negative and positive associations observed between SO_2 concentrations and hospital admissions for respiratory disease. Only a few of the negative associations reached significance. The authors suggest this may be due to the low levels of SO_2 (24 hour mean Amsterdam: 11 ppb; Rotterdam: 15 ppb) and low admission counts during the study (Study ID ●353).

Tenias et al. (1998) found no significant associations between incremental 10 ppb increases in SO_2 (24-hour mean 10.2 ppb) and emergency room visits for asthma (all confidence intervals included 1.0) in an ecological study in Valencia, Spain as part of the APHEA project. Limitations of the study include exposure assessment and a small number of asthma visits (Study ID ● 425).

Burnett et al. (1999) reported no statistically significant associations between daily hospital admissions for respiratory, cardiac, cerebral vascular, and peripheral vascular diseases and daily 10 ppb incremental increases in SO_2 (mean 5.4 ppb). Small percentage increases in hospital admissions attributed to SO_2 could be almost

entirely explained by other atmospheric variables. Limited detail is reported on the exposure monitoring and confidence intervals are not reported (Study ID ● 454).

Harre et al. (1997) reported no significant association between incremental 1.7 ppb increases in ambient SO_2 levels (baseline exposure 0-15 ppb) in Christchurch, New Zealand and either morning or evening peak expiratory flow rate. Selection bias is a possibility in this study and there is some inconsistency regarding the number of subjects recruited from various methods. Training effects were not considered and exposure assessment was taken from the results of one monitor (Study ID ● 470).

Prescott et al. (1998) reported no statistically significant change in the risk of hospital admissions associated with a 10 ppb incremental increase in SO_2 as a moving average of the previous 3 days in Edinburgh (daily mean 14.5±9.0 ppb; 8.3±5.6) ppb. There is some question regarding the validity of the SO_2 data. This and the limited number of monitoring sites suggest that exposure assessment is a major limitation of this study (Study ID ●473).

Hernandez-Garduno et al. (1997) reported that ambient SO_2 levels were negatively correlated with patient visits to clinics in Mexico City. No further analysis was done on SO_2. Associations and SO_2 concentrations were not reported (Study ID ● 475).

Holmen et al. (1996) reported no statistically significant correlations between emergency department visits for asthma and daily ambient SO_2 levels (mean 1.3 ppb summer; mean 2.6 ppb winter; 24-hour range: 0.1-30 ppb). SO_2 monitoring was well described, but measurements were made 10 m off the ground and not the inbreathing zone of patients. Exposure assessment is a limitation of this study, and outcome classification may be questionable. Confidence intervals were not reported (Study ID ●478).

Sheppard et al. (1999) reported no significant associations between an incremental 10 ppb increase in ambient SO_2 levels (daily mean: 14.5±9.0 ppb; 8.3±5.6 ppb) in Seattle and hospital admissions for asthma. However, there was an association between the control admissions (appendicitis) and SO_2 levels. Statistical significance of results was not reported. Exposure assessment was a limitation in this study and the study authors speculate that local emissions in the vicinity of the monitor influenced SO_2 measurements (Study ID ● 482).

Castellague et al. (1995) reported no statistically significant associations between incremental 9.5 ppb increases in ambient SO_2 levels (daily means summer 40.8; winter 52.0 ppb) and emergency room visits in Barcelona, Spain. There were some issues regarding the diagnosis of asthma and chronic obstructive pulmonary disease, which may have lead to outcome misclassification. Limited detail was reported on SO_2 monitoring and measurement (Study ID ●484).

Industrial

Donoghue and Thomas (1999) examined the effect on hospital presentations for asthma of brief spikes in ambient SO_2 concentrations near copper and lead smelters. No relationship was observed between peak ambient SO_2 concentrations up to 3300 ppb and hospital presentations or admissions for asthma (Study ID ◆ 007).

Zuskin et al. (2000) examined differences in respiratory symptoms in

mail carriers in Croatia exposed to an average of six hours of ambient air pollution with concentrations up to 190 ppb compared with control subjects who were not. They observed an increase in the prevalence of upper airway symptoms and nasal catarrh. Measured ventilatory capacity tests were also lower than expected, particularly FEF_{25}, FEF_{50}, and FVC, in both smokers and non-smokers (Study ID ◆ 009).

A study of nickel smelter workers investigated the prevalence of adverse pulmonary function parameters compared to controls (Holness et al., 1985). An average of 0.47 ppm SO_2 was measured in the nickel smelter. Higher prevalence of cough, dyspnea, lower baseline function, as well as decreases in FVC and FEV_1 over the workweek were observed in the smelter workers compared to controls. Baseline airflow rates and FVC and FEV_1 varied over the workweek with levels of SO_2 and particulate matter. During a smelter shutdown, a slight increase in lung function was observed in both smelter workers and controls (Study ID ◆ 016).

Lung function was measured in temporary workers in greenhouses with SO_2 concentrations ranging between 0.15 and 0.66 ppm (Likas et al., 2001). No significant effects on lung function were observed with temporary work in the greenhouse (Study ID ● 017).

Lawther et al. (1974 a, b, c) did a series of pulmonary measurements every working day for five years on four normal subjects employed in central London. Measurements included FEV_1, MMF, and peak expiratory flow. Day-to-day changes in pulmonary measurements were compared with ambient levels of smoke and SO_2. MMF showed the most consistent association with pollution levels. Respiratory infections had a substantial effect on pulmonary measurements. Outdoor exercise had some association with decreases in FEV_1 and MMF. However, associations between pulmonary measures and pollution levels were generally not consistent, even for seasonal variations. None of the associations were reported to be significant (Study ID ● 029, 30, 31).

Case-reports

Several case-reports outline the effects of sudden, accidental exposure to high levels of SO_2.

Harkonen et al. (1983) report the experiences of seven men accidentally exposed to high concentrations of SO_2 in a pyrite mine explosion. Exposure concentrations are unknown and duration of exposure was estimated at 20 to 25 minutes. Nine men were initially exposed. Two subsequently died. Immediately following exposure, thoracic pain and coughing were observed. One week after exposure, the greatest decreases in FVC, FEV_1 and MMFR were observed. No further decrement in lung function was observed by three months after the exposure. Four years after the exposure, the lung function of the workers increased, but never up to pre-accident levels. Four of seven workers showed signs of bronchial hyperreactivity (Study ID ● 021). Piirila et al. (1996) report a subsequent follow-up with the same subjects at 13 years post-exposure. Of the six surviving workers, one had normal spirometry, two had obstruction, and three had obstructive and restrictive ventilatory impairment. A histamine challenge test was performed. One worker could not perform the test due to bronchial constriction. The remaining five workers

showed bronchial hyperreactivity (Study ID ◆ 001).

Rabinovitch et al. (1989) report the cases of two miners exposed to high concentrations of SO_2 in a mine explosion. Three weeks after the incident, both miners showed evidence of severe airway obstruction, hypoxemia, reduced exercise tolerance, and evidence of active inflammation. Over the next 12 months, some improvement in lung function was observed. However, no subsequent improvement was observed three years after the exposure incident (Study ID ◆ 272).

Woodford et al. (1979) present the case of a previously healthy, non-smoking young man exposed to a short, but high concentration of SO_2 (concentrations unknown). Immediately during and after exposure, rhinorrhea, cough, and pulmonary edema were observed with subsequent development of severe, irreversible pulmonary obstructive syndrome. The man was treated with oxygen and released with a clear chest roentgenogram. After a few days, progressively worse dyspnea and severe cough were noted. Upon re-hospitalization, hyperinflation, coarse basilar rales, purulent sputum, and dyspnea at rest were noted. The patient was monitored over a three-year period and the symptoms appeared to stabilize. However, he was diagnosed with persistent obstructive airways disease including forced expiratory wheezing (Study ID ● 269). Charan et al. (1979) observed five subjects who sustained exposure to high concentrations of SO_2 (actual concentrations unknown) in an industrial accident. Two of the five died immediately. The three survivors were subjected to lower concentrations and underwent pulmonary function testing at regular intervals after the incident. Acute symptoms of the three survivors included irritation and soreness of the throat, tightness in the chest, and intense dyspnea, as well as decreased breath sounds, and diffuse rales. Subsequent tests indicated severe irreversible airway obstruction in one subject and mild airway obstruction in another subject. The fifth subject, a firefighter who had been wearing respiratory apparatus at the time of exposure, showed no acute or chronic pulmonary function abnormalities (Study ID ● 270).

Galea (1964) reported the case of a 35-year old man who died 17 days after accidental exposure to high levels of SO_2. Several days after exposure, the man was discharged from hospital in satisfactory condition. 10 days after discharge, the man was re-admitted with dry, irritable, tiresome cough, dyspnea, copious amounts of mucus, rales on both lung bases, and audible wheezing. The man died in hospital. An autopsy revealed a uniformly marble appearance and a feathery, pillowy consistency of the lungs. In addition, there was extensive tracheobronchitis, airway lesions, intense submucosal gland activity, and extension of alveoli and air sacs (Study ID ● 271).

Respiratory System – Biochemical

Most of the studies investigating the effects of SO_2 on pulmonary biochemistry did so in an effort to increase understanding of the mechanism of action. The clinical significance of reported biochemical effects is often uncertain and not discussed in the studies.

Clinical studies

Speizer and Frank (1966a) measured the absorption and desorption of SO_2 in the

upper respiratory tracts of healthy subjects breathing by nose. They observed that SO_2 concentration in the respiratory tract decreased upon inspiration (from 16.1 ppm in the breathing mask to 13.8 ppm inside the nose to undetectable in the oropharynx). Expired gas in the pharynx was virtually free of SO_2, but expired gas exiting the nose had picked up 2.0 ppm SO_2. They concluded that SO_2 is removed by the nose during inhalation and some is desorbed on exhalation (Study ID ◆ 033).

Field et al. (1996) investigated the mechanism of SO_2-induced bronchoconstriction in asthmatic subjects by exposing them to 0.5 to 8.0 ppm SO_2 with and without previous exposure to an opioid or a cyclooxygenase inhibitor. Response was measured as the dose of SO_2 required to induce a 35% fall in specific airways conductance. SO_2 responsiveness decreased with the opioid and increased with the cyclooxygenase inhibitor (Study ID ◆ 052).

Bechtold et al. (1993) exposed adult asthmatics to either 1 ppm or 7 ppm SO_2 for 10 to 20 minutes every other day for three weeks to investigate the S-sulfonate levels in nasal lavage fluid as a potential biomarker of SO_2 exposure. They found that S-sulfonate levels were statistically significantly elevated relative to control group levels. However, the levels did not accumulate over time, suggesting continuous clearance from the nasal passages. The levels of S-sulfonate observed in the nasal lavage fluid are approximately three orders of magnitude higher than levels measured in plasma after exposure to similar concentrations of SO_2, suggesting that S-sulfonate in nasal lavage fluid could be a good short-term biomarker for SO_2 exposure (Study ID ◆ 066).

Sandstrom et al. (1989a) used bronchoalveolar lavage (BAL) fluid to investigate the effect of SO_2 on the healthy human lung. 24 hours after exposure to 4 ppm SO_2 for 20 minutes, increased alveolar activity was observed in BAL fluid. Even greater alveolar activity as well as increased numbers of macrophages and lymphocytes were observed 24-hours after exposure to 8 ppm for 20 minutes. After both exposures, all cell activity returned to normal within 72 hours (Study ID ◆ 083). Further study found significant increases in lysozyme-positive macrophages, lymphocytes, and mast cells in BAL after exposure to 8 ppm SO_2 for 20 minutes during exercise (Sandstrom et al., 1989b). Peak values were observed 24 hours after exposure and cell numbers returned to pre-exposure values within 72 hours (Study ID ◆ 090). A dose-dependent increase in the number of mast cells, lymphocytes, lysozyme-positive macrophages and total number of macrophages was observed in BAL fluid after exposures to 4, 5, and 8 ppm for 20 minutes, but not up to 11 ppm (Sandstrom et al., 1989c) (Study ID ● 091).

Witek and Schachter (1985) investigated the mechanism of SO_2 bronchoconstriction by exposing mildly asthmatic subjects to 1 ppm SO_2 for 40 minutes and to methacholine. They found a significant correlation between the dose of SO_2 and the dose of methacholine required to reduce flow rates to 60% of vital capacity. The authors postulate that there is a relationship between the mechanism of response to SO_2 and to methacholine (Study ID ◆ 085).

Lazarus et al. (1997) postulate that cysteinyl leukotrienes contribute to the bronchoconstriction seen in asthmatics during SO_2 exposure. They found that the leukotriene receptor antagonist zafirlukast inhibited SO_2-induced bronchoconstriction in 12 subjects exposed to up to 8.0 ppm SO_2 for 4 minutes, supporting their postulation (Study ID ◆ 321).

Non-clinical studies

Guinea pigs

Riedel et al. (1988) exposed guinea pigs to between 0.1 and 16.6 ppm SO_2 for 8 hours a day for 5 consecutive days to investigate the effect of SO_2 exposure on bronchial sensitivity to inhaled antigen. 67% to 100% of the SO_2-exposed animals exhibited positive bronchial reactions to inhaled antigen compared to only 7% of the control animals. In addition, the extent of bronchial obstruction as well as concentrations of antigen-specific antibodies in serum and bronchoalveolar fluid were greater in animals exposed to SO_2 at all levels compared to controls (Study ID ◆ 133).

Haider (1985) investigated the lipid metabolism in the organs of guinea pigs exposed to 1 hour of 10 ppm a day for 30 days. Increased concentrations of cholesterol, total lipids and gangliosides and a decrease in phospholipids were observed (Study ID ◆ 163).

Atzori et al. (1991) investigated the mechanism of SO_2-induced bronchoconstriction using guinea pig lungs. Guinea pigs were exposed to 250 ppm SO_2 for 10 minutes after treatment by a cyclooxidase inhibitor or an H1-receptor agonist. Neither compounds attenuated the SO_2-induced bronchoconstriction, suggesting that the bronchoconstriction is a result of a local effect on sensory nerves, possibly dependent on the release of sensory neuropeptides (Study ID ◆ 178).

Halinen et al. (2000) examined the effects of exposing guinea pigs to ten minutes each of 1, 2.5, or 5 ppm SO_2 in cold air. In the group exposed to cold air with SO_2 there was a significantly lower proportion of macrophages in BAL white cells in comparison to the group exposed to cold air without SO_2 (Study ID ◆ 245).

Hajj et al. (1996) exposed Dunkin Hartley guinea pigs to 500, 1000, 1500, and 2000 ppm SO_2 to investigate the role of tachykinins in the bronchoconstriction response. They concluded that tachykinin release from sensory endings does play a role in SO_2-induced bronchoconstriction in anaesthetized guinea pigs. Exposure duration was not clearly stated. There is limited information on the experimental conditions and design (Study ID ● 370).

Ito et al. (1995) exposed Hartley guinea pigs to 800 ppm for 2 hours and observed that direct epithelial injury from SO_2 inhalation results in loss of epithelial cells and an increase in permeability. In addition, they suggest that inflammatory cells may promote rather initiate bronchial responsiveness. The information provided in the paper suggests that Good Laboratory Practice guidelines were not followed (Study ID ● 452).

Rats

Kahana and Aronovitch (1968) investigated the effects of SO_2 exposure on pulmonary surface tension. After exposure to 800 ppm SO_2 for 3 hours, a small but significant reduction in maximal and minimal surface tension but no respiratory distress or pathological changes in the lungs were observed. After exposure to 1225 ppm

for 2 hours, pulmonary edema was observed. In addition, two of the rats exhibited severe and persistent dyspnea while the others had transitory and less severe respiratory difficulty. There was a greater drop in surface tension at the higher exposure (Study ID ◆ 155).

Vai et al. (1980) investigated the effects of exposure to 600 ppm SO_2 for 30 to 100 hours on rat tracheobronchial epithelium. They observed a considerable increase in mucosal permeability in the tracheal epithelium and epithelium of the main bronchi both in vivo and in vitro. This increase was reduced but still present three months post-exposure (Study ID ◆ 206).

Langley-Evans et al. (1996) investigated the potential of SO_2 to be a glutathione (GSH) depleting agent. Rats were exposed to SO_2 concentrations between 5 and 100 ppm for 5 hours a day for 7 to 28 days. The lowest concentrations (5ppm) did not result in lung injury or inflammation, but levels of GSH were lower in the lung, liver, heart and kidney. In addition γ-glutamylcysteine, glutathione peroxidase, glutathione S-transferase, and glutathione reductase activities were all reduced. At 100 ppm there was evidence of lung inflammation and GSH levels were lowered as well as enzyme activity. However, at 50 ppm, GSH levels were the same relative to controls, although enzyme activity was lowered (Study ID ◆ 251).

Husain and Dehnen (1978) examined the effect of SO_2 on benzo(a)pyrene metabolism in the lungs of rats exposed to 46.5 ppm continuously for up to 4 weeks. Benzo(a)pyrene metabolism was measured as the activity of aryl hydrocarbon hydroxylase (AHH). No change was observed in AHH activity between the exposed and control animals (Study ID ◆ 252).

The effect of SO_2 exposure on four rat enzyme systems was investigated by Barry and Mawdesley-Thomas (1970). After exposure to 300 ppm SO_2 for six hours a day for 10 days, the acid phosphatase activity in the free alveolar cells of the lung parenchyma was markedly increased. There was also a slight increase in the activity of β-glucuronidase, β-galactosidase, and N-acetyl-β-glucosaminidase in some free alveolar cells in the peribronchiolar region (Study ID ● 181).

Gause and Barker (1978) exposed rats to SO_2 concentrations from 5 to 20 ppm continuously for a week to investigate the uptake of SO_2 in the nasal mucus and the subsequent effects on the electrophoretic properties of nasal mucus glycoproteins. In the first 30 minutes of exposure, 90% of the inhaled SO_2 remained in the nasal mucus with 10% found in the plasma or serum. The ratio of SO_2 concentrations in the mucus to those in the serum leveled off after 1 to 4 hours of exposure to approximately 3:1. Electrophoretic gels of nasal mucus were collected immediately following exposure as well as at 8 days post-exposure. A dose-related increase in new bands on the electrophoretic gels were observed at both times, suggesting polymerization of mucus glycoproteins (Study ID ● 193).

To investigate the effects of SO_2 exposure on the surface properties of lungs, rats were exposed to 627-751 ppm SO_2 for either a single 3-hour exposure or 9 exposures of 4 hours each at 257-450 ppm (Kahana and Aronovitch, 1966). A reduction of surface forces and a decrease in mean transpulmonary pressures was observed in the single exposure animals. Changes in surface properties were unclear in the multiple exposure group due to differences in

characteristics between the exposure and control groups (Study ID ● 262).

Mice

In an investigation of the effect of SO_2 on the pathogenesis of upper respiratory viral infection, mice were exposed to 0.03 to 0.1 ppm SO_2 for four weeks (Ukai, 1977). The inflammatory response to the virus was more rapid and severe in SO_2-exposed mice than in those not exposed to SO_2. In addition, regeneration and antibody appearance were initiated sooner and the HI titer developed more rapidly and reached higher levels in the exposed mice than the non-exposed mice. Animals that were exposed to SO_2 but not infected with the virus exhibited a sixfold increase in the number of goblet cells in the nasal epithelial cells (Study ID ◆ 207).

Hamsters

Skornik and Brain (1990) investigated the effect of exercise and 50 ppm SO_2 exposure on pulmonary macrophage endocytosis in Syrian golden hamsters. A significant reduction was observed only after 40 minutes of continuous running while breathing 50 ppm SO_2. There were no changes with non-exercise exposure to SO_2 or between exercise and no exercise without SO_2 exposure (Study ID ▲ 374).

Squirrels

Biochemical changes were investigated in the trachea, lungs and heart of squirrels exposed to 500 ppm SO_2 for 5 minutes (Rana et al., 1979). Changes in lung lipids caused changes in the surface tension of the lungs. In addition, membrane permeability was altered, resulting in changes in protein content (Study ID ● 147).

Chickens

Majima et al. (1985) investigated the elastic recoil distance both *in vivo* and *in vitro* of nasal mucous from chickens exposed to 6 ppm SO_2 for 16 hours a day for 7 days. They observed a decrease in the recoil distance *in vivo*, but not *in vitro* after SO_2 exposure (Study ID ● 149).

Okuyama et al. (1979) exposed chickens to levels of SO_2 ranging from 3.4 to 18.5 ppm for between 1 and 14 days to investigate any histological changes in the tracheal mucosa. At all exposure levels, there was an increase in infiltrating mononuclear and polymorphonuclear cells, acid phosphatase positive cells, the number of plasma cells and lymphocytes, acid mucins, and in the number of mitotic figures. There were also changes in mucus type and a decrease in neutral mucins. At the highest concentration (18.5 ppm), the mucosa-to-wall ratio doubled and some mucosal damage was observed (Study ID ● 199).

Bauer (1981) exposed chickens to 350 to 400 ppm SO_2 for three hours to investigate the biochemistry of tracheobronchial secretions. A significantly increased mucus output (320%) was observed in the chickens exposed to SO_2 compared to controls; however, glycoprotein output increased by only 50%. Therefore, the glycoprotein concentration was lowered to approximately one third of the concentration in the control group. No differences were observed in the carbohydrate pattern of the glycoproteins between the exposed and non-exposed chickens (Study ID ● 221).

Dogs

Man et al. (1986) investigated the effect of SO_2 exposure on the bioelectric and barrier properties of the tracheal epithelium. After exposure to 100 ppm SO_2 for 75 minutes, there were few bioelectric changes in the trachea of dogs. However, after exposure to 500 ppm for the same amount of time, adverse changes to the bioelectric properties were observed, as well as nonelectrolyte permeability (Study ID ◆ 150).

No effects observed
Azoulay et al. (1980) examined the effects of continuous exposure for 1 to 49 days to 2 ppm SO_2 alone and in mixtures with 2 ppm NO and NO_2 on lung structure and blood-oxygen affinity in rats. They observed no difference in blood erythrocyte variables and oxyhemoglobin dissociation curves between exposed animals and controls for any gases or mixtures of gases. No changes in lung structures were observed (Study ID ◆ 225).

Epidemiology
No epidemiology studies reported biochemical effects.

Respiratory System – Structural

Clinical studies
Kienast et al. (1994a) investigated the effect of SO_2 at different concentrations on ciliary beat frequency. Cells taken from volunteers' noses were exposed for 30 min to 2.5 to 12.5 ppm at 37°C and 100% humidity. A dose-dependent decrease in ciliary beat frequency was observed from low to high concentrations of SO_2 (Study ID ◆ 320).

In a similar study, Kienast et al. (1996) exposed cells taken from the noses of 12 healthy volunteers to 0, 2.5, 5.0, 7.5, 10.0, and 12.5 ppm for 30 minutes. A dose-dependent decrease in ciliary beat frequency was observed, suggested to be a result of the increase in hydrogen ion concentration in the culture medium (Study ID ● 427).
Riechelmann, et al. (1994) observed a concentration–dependent reduction in ciliary beat frequency in human nasal cells following exposure to 2.5, 5, 7.5, 10, and 12.5 ppm SO_2 for 30 and 120 minutes (Study ID ● 466).

Carson et al. (1985) examined the appearance of compound cilia in the nasal mucosa in normal human subjects following exposure to 0.75 ppm for 2 hours. They observed increases in the prevalence of compound cilia and a statistically significant association between SO_2 exposure and compounding of nasal epithelial cilia. They postulate that compound cilia are an acquired defect that could be used as a possible biomarker of SO_2 exposure (Study ID ● 046).

Non-clinical studies
Guinea pigs
Riechelmann et al. (1995) looked at correlations between functional alterations and morphological changes of the mucociliary system following SO_2 exposure. Guinea pigs were exposed to concentrations of 3, 6, 9, and 14 ppm for 30 minutes. There was a dose-dependent decrease in mucociliary activity in the exposed animals. However, only minor morphological changes were observed at the lowest exposure level. At higher exposure levels, epithelial sloughing, intracellular edema and mitochondrial swelling, ciliary cytoplasmic extrusions

and a widened intercellular space were observed (Study ID ● 132).

Rats

Knauss et al. (1976) exposed rats to 600 and 700 ppm SO_2 for 3 hours a day equaling 9, 18, or 30 hours of cumulative exposure. A significant increase in the amount of solid material recovered by bronchial lavage was observed with increasing exposure time (Study ID ◆ 250).

Stratmann et al. (1991) exposed Wistar rats to 800 ppm SO_2 for 8 hours and observed the effects on the tracheal epithelium via electron microscopy. They observed a gradient of decreasing damage in the tracheobronchial tree in the peripheral direction. The most severe lesions (detached and necrotic cells and missing cilia and goblet cells) were observed in the trachea epithelium. The clinical significance of these results is unclear (Study ID ◆ 305).

Gross et al. (1969) exposed rats to very high concentrations of SO_2 (2500 and 4000 ppm) for 15 minutes to determine any morphologic evidence of alveolar edema. Evidence of edema was found in the separation of the surface epithelium from the alveolar septum, suggesting that development of edema was very rapid (Study ID ● 166).

Pariente (1980) studied the permeability of rat tracheobronchial epithelia both *in vivo* and *in vitro*. Rats were exposed to 600 ppm SO_2 for 100 hours or 1000 ppm for 4 hours. The four hours exposure to 1000 ppm was not lethal, but induced acute bronchitis and bleeding of the rhinopharynx. Chronic tracheobronchial injuries were observed after 600 ppm for 100 hours. After three months in a clean-air atmosphere, recovery was complete. However, there was increased permeability of the tracheobronchial epithelium both *in vivo* and *in vitro* (Study ID ● 210).

Hong (1996) observed no significant changes in cell count, LDH, total protein, CC16, and lysozyme in bronchoalveolar lavage fluid in rats exposed to 30 or 50 ppm for 4 or 12 hours. Details of the experimental methods were lacking (Study ID ● 447).

Farone et al. (1995) reported substantially increased numbers of polymorphonuclear leukocytes in rat tracheas after 1 day of exposure to 230 ppm SO_2. The study attempted to discover a mechanism for SO_2-induced chronic bronchitis. The study did not follow Good Laboratory Practice guidelines (Study ID ● 477).

Mice

Giddens and Fairchild (1972) examined mice from a defined flora colony with no disease (DF) and conventional mice with mild upper respiratory tract disease (CO) after exposure to 10 ppm SO_2 for 4 to 72 hours. After 24 hours of exposure, the olfactory mucosa was reduced to half the thickness seen in the control animals. In addition, olfactory hairs were smaller in number and height than controls. The CO mice at 24 hours exhibited complete necrosis of the olfactory mucosa. After 48 to 72 hours, DF mice exhibited severe rhinitis accompanied by serous exudation in the nasal cavity and desquamation of respiratory epithelial cells. The CO mice exhibited greater necrosis of the nasal mucosa at 48 to 72 hours than at 24 hours (Study ID ◆ 191).

Weiss and Weiss (1976) found a statistically significant increase in static lung compliance in mice after exposure to 40 ppm SO_2 for 6 to 9 days. Other effects were not statistically significant (Study ID ● 208).

Min et al. (1994) observed increasing injury to the olfactory epithelium in ICR mice as the duration of exposure to 20 ppm SO_2 increased from 30 to 60 to 120 minutes. Injuries included edema, loss of cilia, epithelial thinning, and epithelial desquamation in mice exposed for 60 and 120 minutes. No changes were observed in mice exposed for 30 minutes. Little detail is given on the experimental methods of treatment of animals as per Good Laboratory practice guidelines (Study ID ● 287).

Hamsters

Asmundsson et al. (1973) investigated the morphologic changes produced by repeated injury to airway epithelial cells by SO_2 and the time course of those changes. Hamsters were exposed to concentrations of 40, 100, 200, 250, and 400 ppm for 5 hours a day, five days a week for six weeks. Animals were examined frequently to assess time of any changes seen. Epithelial damage was observed in large airways at all levels of exposure after 1 week. A sequence of changes from loss of cilia at 1 to 2 days of exposure to squamous metaplasia after 2 to 4 weeks was observed at concentrations above 100 ppm (Study ID ● 198).

Rabbits

Blanquart et al. (1995) observed significant ultrastructural alterations of ciliated cells after a 1-hour exposure to 10 and 30 ppm SO_2 in Fauve de Bourgogne rabbits. Ciliary activity was significantly inhibited. These findings suggest a mechanism of action of SO_2 toxicity (Study ID ◆ 463).

Dalhamn and Strandberg (1961) reported no effect on ciliary movement in rabbit trachea after inhalation of 200 ppm SO_2 for 45 minutes. However, ciliary movement stopped when 10 ppm SO_2 or greater was blown directly onto the trachea. Information on the experimental protocol was lacking (Study ID ● 294).

Strandberg (1964) reported differences in the absorption of high concentrations of SO_2 and low concentrations in the respiratory tract in rabbits. Concentrations ranged from 0.05 to 700 ppm; however, there is very little detail given regarding the dosing regime or exposure duration. Other information on the experimental protocol is also lacking (Study ID ● 417).

Dogs

Frank et al. (1967) investigated the uptake of $^{35}SO_2$ into various body fluids in dogs exposed to 22±2 ppm for 30 to 60 minutes. There was limited detail on the experimental protocol and Good Laboratory Practice guidelines were not followed (Study ID ● 286).

Balchum et al. (1959) reported that dogs breathing $^{35}SO_2$ through the nose and mouth retained a smaller proportion of the inhaled gas in the trachea, lungs, hilar lymph nodes and liver and spleen than dogs breathing similar concentrations via tracheostomy. However, only one dog was exposed to each exposure level (1.1 to 141 ppm) and duration (20 to 40 minutes) and details on all areas of the experimental protocol are lacking (Study ID ● 418).

Human in vitro studies

Knorst et al. (1996a) reported functional impairment of human alveolar macrophages after exposure to 1.0, 2.5, and 5.0 ppm SO_2 for 30 minutes. The clinical and toxicological significance of the results was not clear (Study ID ◆ 308).

Knorst et al. (1996b) observed changes in alveolar macrophage and blood

monocytes chemotactic activity upon exposure of human macrophages from subjects with bronchial carcinoma to 0.5, 1.5, and 2.5 ppm SO_2 for 15 minutes. Cell viability was not affected. The clinical significance of these results is unclear, as it cannot be assumed that in vivo studies would produce the same results (Study ID ● 319).

Epidemiology

No epidemiology studies were found that reported solely structural effects of SO_2 exposure. Any structural effects were reported as the cause of functional effects found only after autopsy. These results were considered in the section ***Respiratory system-Functional.***

Respiratory System – Signs and Symptoms

Several studies focussing on other respiratory effects also reported signs and symptoms of respiratory distress.

Clinical studies

Effects observed

Adult human subjects were exposed to SO_2 concentrations between 0.5 and 5 ppm for 1 to 5 minutes both with and without exercise (Kreisman et al., 1976). Breathing was through the mouth. After a 3-minute exposure to 3 ppm or 5 ppm either at rest or during exercise, 15 of 18 subjects reported dryness, irritation or burning of the throat. Frequently, subjects would report an urge to cough immediately after SO_2 inhalation. Symptoms were also reported when breathing air without SO_2, but not when breathing 0.5 ppm or 1.0 ppm SO_2 (Study ID ◆ 039).

Andersen et al. (1974) investigated the human response to controlled levels of SO_2. They exposed adults to between 1 and 25 ppm SO_2 for 6 hours a day for three consecutive days. Discomfort was reported, proportional to SO_2 concentration (Study ID ◆ 063).

Balmes et al. (1987) investigated the relationship between bronchoconstriction in asthmatic adults and the duration and concentration of SO_2 exposure. Subjects were exposed to 0.5 and 1.0 ppm for 1, 3, and 5 minutes. After exposure to 1.0 ppm for 1 minute, a quarter of the subjects developed chest tightness. After exposure to 0.5 ppm for 3 and 5 minutes or exposure to 1.0 ppm for 3 minutes, seven of eight subjects showed wheezing, chest tightness and dyspnea, and used an inhaled bronchodilator (Study ID ◆ 064).

Witek et al. (1985) investigated subjective responses to concentrations of SO_2 less than 1 ppm for 40 minutes in healthy and asthmatic subjects. Asthmatics reported chest tightness, wheezing, dyspnea and cough, while the healthy subjects reported taste and odour complaints. There was an increase in the number and severity of the complaints associated with increasing concentration (Study ID ◆ 093).

No effects observed

Kagawa (1983) observed no symptoms in healthy adults after exposure to 0.15 ppm SO_2 for 2 hours with intermittent light exercise (Study ID ◆ 072).

Non-clinical studies

Amdur (1954) observed few signs of respiratory distress in guinea pigs exposed to 89 ppm SO_2 for 8 to 16 hours (Study ID ● 125).

Matsumura (1970) exposed guinea pigs to 20, 60, 180, and 330 ppm SO_2 for 30 minutes. Signs of irritation, such as

sneezing, rubbing eyes or noses, or uneasiness in the animals were observed only after exposure to 330 ppm. Signs of irritation disappeared within a few minutes of exposure. There were no significant signs of respiratory distress (Study ID ● 142).

Matsumura et al. (1972) examined the effects of pre-exposure to SO_2 and other air pollutants on the sensitivity of guinea pigs to inhaled acetylcholine. Guinea pigs were exposed to 450, 600, and 700 ppm for 30 minutes. No differences in respiratory signs were observed between the control group and the groups exposed to SO_2 at any concentration (Study ID ● 144).

Epidemiology studies

Effects observed

Cohen et al. (1974) carried out a telephone survey to investigate the reporting of irritative symptoms during well-publicized and unpublicized periods of moderately elevated air pollution (peak hourly SO_2 = 0.11 to 0.15 ppm) and a period of low pollution (peak hourly SO_2 = 0.02 to 0.04 ppm). Significant increases in eye irritation, throat irritation, chest discomfort, shortness of breath, restricted activity, and medical visits were observed during both elevated pollution episodes compared to the control (low pollution) period. ORs and confidence intervals were not reported (Study ID ◆ 011).

Carnow et al. (1969) investigated a potential dose-response relationship between levels of pollution as measured by SO_2 concentrations and respiratory morbidity in patients with chronic bronchopulmonary disease. SO_2 concentrations were measured at up to 0.30 ppm over the 10 month study period. They observed a dose-response association between SO_2 concentrations and percent person-days of illness; the rate of illness was 50% greater on days when SO_2 concentrations were 0.25 ppm than on days when SO_2 concentrations were 0.04 ppm or lower. Associations and confidence intervals were not reported (Study ID ◆ 010).

A study of nickel smelter workers investigated the prevalence of adverse pulmonary function parameters compared to controls (Holness et al., 1985). An average of 0.47 ppm SO_2 was measured in the nickel smelter. Higher prevalence of cough, dyspnea, and lower baseline function over the workweek were observed in the smelter workers compared to controls. Associations and confidence intervals not reported (Study ID ◆ 016).

No effects observed

Love et al. (1982) investigated the effect of increased exposure to SO_2 on respiratory illness in the Great Salt Lake basin, Utah. Annual mean ambient SO_2 concentrations were measured to be between 15 and 30.5 ppb. No relationship was observed between higher SO_2 concentrations and respiratory illness (Study ID ◆ 015).

Hoek and Brunekreef (1993) investigated the effect of winter air pollution episodes on respiratory effects of children. SO_2 concentrations were measured to be between 0 and 38 ppb. No association was observed the prevalence of acute respiratory symptoms and the concentrations of SO_2 or other compounds (Study ID ◆ 018).

Franklin et al. (1985) did an epidemiology study to investigate the health effects of acute exposure to transported air pollutants in asthmatic and non-asthmatic children. The study lasted 10 days and the levels of SO_2

were not reported. No statistically significant health effects were observed in relation to SO_2 (Study ID ● 004). Ayres et al. (1989) investigated the respiratory health effects of an acid transport event in January 1985 in the United Kingdom. SO_2 levels were measured to be between 19 and 40 ppb in a polluted area and 13 to 27 ppb in an unpolluted area. No increase in respiratory morbidity was observed between the two areas (Study ID ● 006). Complaints of shortness of breath, frequent colds, cough, sore throat, and chest tightness prompted a Health Hazard Evaluation of Portland cement plants to assess whether SO_2 exposure was the genesis of the problems (NIOSH, 1984). SO_2 levels at the plants were measured to be 1.03 ppm at one plant and between 0.2 and 1.8 ppm at another (Study ID ● 267).

Respiratory System – Other

Fairchild et al. (1972) investigated the effect of exposure to SO_2 on influenzal pneumonia in mice. Mice were exposed to concentrations ranging between 3.4 and 34.5 ppm continuously for up to 7 days. When SO_2 was administered after virus exposure, significantly increased incidence of pneumonia was observed at 19 ppm and greater. When the virus was administered after SO_2 exposure, a significant increase in pneumonia incidence occurred only at 25 ppm after 4 to 7 days of exposure. Histopathological effects were observed at SO_2 concentrations of 27 ppm and greater after 7 days of continuous exposure (Study ID ◆ 182).

Suzuki (1969) exposed guinea pigs to 10 and 50 ppm SO_2 for 3 hours to compare the lung histamine and water content of exposed and non-exposed animals. No effect on water or histamine content of the lungs was observed at either exposure level (Study ID ● 126).

Frank et al. (1969) investigated the uptake and desorption of $^{35}SO_2$ in the nose and mouth of dogs exposed to SO_2 concentrations between 1 and 50 ppm for 1.5 to 5 minutes. Virtually all the $^{35}SO_2$ was absorbed by the nose at all concentrations and times. Absorption by the mouth was concentration-dependent. Desorption was observed only from the mouth, with release of $^{35}SO_2$ gas observed up to 25 minutes post-exposure (Study ID ● 169).

Summary

The largest number of studies and consequently the most convincing evidence for adverse health effects of SO_2 exposure was found in effects on the respiratory system. Please refer to Tables 1 though 9 and Figures 1 to 7 for further summary.

Clinical

Of the 96 clinical studies investigating respiratory effects, 73 (76%) were ranked high or moderate.

Healthy subjects

There were no high quality studies looking at healthy humans in the time range of 1 to 10 minutes of exposure. There were, however, a number of moderate quality studies. Pulmonary effects in healthy humans starting at 0.75 ppm and up to 15 ppm were observed in clinical studies. These studies involved direct exposure to SO_2 with hyperventilation and/or exercise. There is some evidence that pulmonary effects are greater when exposure is through a mouthpiece (orally) than through the nose. Dryness, irritation and burning of the throat were observed at 3,

15, and 28 ppm in two moderate quality studies.

Asthmatic subjects
Only one study of 27 investigating exposure for 1 to 10 minutes was rated high quality. This study noted a concentration-dependent change in respiratory function in asthmatics between 0.5 and 1 ppm with exposure during light to heavy exercise. The moderate quality studies also involved direct exposure, usually with exercise and/or hyperventilation. Small but significant pulmonary effects were observed in asthmatics at concentrations ranging between 0.1 ppm to 10 ppm. These effects were transitory and pulmonary function returned to normal after exposure ceased. Again, there is evidence that mouth breathing or oral exposure results in a great effect than nasal exposure.

Healthy subjects
Pulmonary effects were observed at concentrations as low as 1 ppm at exposures times between 11 and 30 minutes. Again, these effects were transitory. Three studies investigated the effects on cells from the respiratory system after exposure to concentrations between 2.5 and 8 ppm. Some effect was observed on these cells.

Asthmatic subjects
Again, only one study was ranked high for exposures between 11 and 30 minutes. Pulmonary function effects were observed in asthmatics upon exposure to 0.5 ppm SO_2 with moderate exercise.
Other studies suggest pulmonary effects with exercise at concentrations between 0.1 ppm and 1 ppm.

The weight of evidence for exposures up to 30 minutes suggests that healthy humans can experience exposures to SO_2 up to 10 ppm with only transitory effects on pulmonary function, even under challenging conditions involving hyperventilation, mouth-only exposure, and heavy exercise. Transitory effects may be observed at concentrations as low as 0.75 ppm.

For exposures up to 30 minutes, asthmatics appear to demonstrate pulmonary effects at lower thresholds (0.1 ppm), although even in this population subgroup the clinical effects are transient and may or may not require intermittent pharmacologic intervention.

Few studies investigated exposures in asthmatics longer than 30 minutes. Those that did reported transitory pulmonary function effects at exposure levels of 0.50 to 1 ppm. The studies investigating healthy subjects at these longer time ranges investigated concentrations between 0.75 and 25 ppm. A concentration-dependent response in discomfort was reported between 1 and 25 ppm. Transitory effects on pulmonary function and nasal mucous flow were reported up to 5 ppm at these longer time ranges.

The weight of evidence for single exposures up to 4 hours and repeated exposures between 3 days and 3 weeks suggests that transitory pulmonary effects might be expected for asthmatics at exposure concentrations between 0.5 and 1 ppm and for healthy humans between 0.75 and 25 ppm, with some evidence for a concentration-dependent response in healthy subjects.

Non-clinical

Of the 93 non-clinical studies investigating respiratory effects, 39 (42%) were ranked high or moderate. These studies looked at a variety of species and health outcomes. In addition there was substantial variation in the concentrations and exposure times investigated. Exposures included single exposures of a few hours or less to several days as well as multiple exposures of a few hours per day for up to 30 days.

The concentrations in studies of animals exposed for ***up to 2 hours*** *ranged between 0.5 ppm and 1000 ppm. For concentrations up to 100 ppm, effects reported were predominantly very mild respiratory effects and changes at the cellular or ciliary level. Above 100 ppm, greater pulmonary effects were in evidence, with indications of changes to the lung. There is evidence of increasing severity of effect with increasing concentration.*

In studies with exposures ***between 2 and 24 hours****, mild respiratory effects and delayed airway reactivity were reported with concentrations up to 40 ppm. Damage to the lungs was reported at concentrations of 800 ppm and 1225 ppm.*

At exposures ***between 1 and 7 days****, slight changes were observed in lung function and in response to virus challenges at concentrations of 0.1 ppm to 34.5 ppm. At the higher concentrations of 100 ppm and 600 ppm, changes to lung structure were reported.*

Five studies investigated exposures ***between 7 and 30 days****. One study reported changes in response to virus challenges with exposures up to 0.1 ppm for 4 weeks. The other four studies reported changes in lung biochemistry and some decrease in pulmonary function at concentrations between 10 and 600 ppm.*

Epidemiology

Of the epidemiology studies and case reports investigating respiratory effects, less than half were ranked moderate. There were no high quality epidemiology studies.

The limitations of these epidemiology studies are similar to those outlined in the mortality section.

Epidemiology studies were divided into two types based on calculation of exposure concentration. One set of studies calculated exposures as increases in ambient concentration above a baseline or average concentration. These studies report results as an increase in outcomes (e.g. hospital admissions for asthma) per increase in ambient concentration. For example, a study might report results as a 1.6% increase in hospital admissions for every 3.5 ppm increase in ambient SO_2 concentration. Another set of studies reported exposure as discrete concentrations, either as average concentrations or a concentration range. These studies might report results as, for example, 7% more admissions during periods of higher pollution.

A weight of evidence evaluation is difficult for the epidemiology studies as the majority of the epidemiology studies were ranked low quality. For the moderate quality studies reporting both types of exposure metric, there was an equal number of studies that found insignificant or no associations between

ambient SO_2 concentration and health outcomes as there were that reported an association.
Deriving causal associations from environmental epidemiologic studies is difficult for a number of reasons. Exposure misclassification is a major limitation of these studies. An additional limitation involves the classification of outcome. In several cases, the respiratory diseases investigated, particularly COPD and asthma, did not have clear case definitions for the purposes of the study, which could lead to inaccurate or inconsistent diagnoses of the health outcomes.
The challenge of different exposure metrics has been discussed. For those studies looking at increases above a baseline, it should be noted that the baseline concentrations differ for each study. In addition, the time-averaging or time over which exposure was calculated is different between studies, making comparisons difficult. The populations used tended to be small and relatively undefined. Most of the studies endeavored to find correlations between ambient levels of SO_2 and rates of health outcomes. Very few calculated relative risks or similar epidemiological statistics. Statistical significance was not calculated in many studies. For those studies that did report statistically significant results, the lower confidence intervals were often very close to one and there were no associations that would be considered strong (OR >2).

F. Signs and Symptoms

Clinical

Effects observed-healthy subjects

Kulle et al. (1986) observed statistically significant increases in nose and throat irritation after exposing adult subjects to 1 ppm SO_2 for 4 hours/day, 3 days/week for 3 weeks (Study ID ▲ 096).

Speizer and Frank (1966b) exposed healthy male subjects to 15 and 28 ppm SO_2 orally or nasally for ten minutes. They observed coughing during the first few minutes in subjects exposed by mouth. These subjects also reported burning sensations of the throat and substernal area for the first five minutes of exposure. Those subjects exposed through the nose had no chest symptoms and little coughing, although they did report some irritation of the posterior pharynx, which lasted for several minutes (Study ID ◆ 054).

Andersen et al. (1974) examined subjective response, among other symptoms, in healthy adult males exposed to between 1 and 25 ppm SO_2 for 6 hours/day for 3 days. Some discomfort, proportional to SO_2 concentration, was reported by the subjects. Subjects with nasal mucus flow rates that were initially slow experienced the greatest discomfort (Study ID ◆ 063).

Toyama and Nakamura (1964) exposed healthy male subjects to concentrations of 1 to 60 ppm SO_2 for 5 minutes. Subjects reported objectionable odours, irritation of the upper respiratory tract, cough, and unusual sensations in the lungs during the first few minutes of exposure (Study ID ● 053).

Sandstrom et al. (1988) endeavoured to establish standardized procedures for exposure to SO_2 in clinical trials and compared mucosal and airway effects from SO_2 vs. air exposure. They exposed eight healthy subjects to 0.4 to 4 ppm SO_2 for 20 minutes. Subjects reported irritation of the throat and an unpleasant smell (Study ID ● 087).

Effects observed-asthmatic subjects
Gong et al. (1995) examined SO_2-sensitive asthmatics to determine the effects of SO_2 exposure up to 0.5 ppm for 1 hour compared to different intensities of exercise on lung function, asthma symptoms, and stamina. They observed that increasing SO_2 levels had greater negative effects on lung function, symptom scores and stamina ratings than did increasing the intensity of exercise (Study ID ▲ 077).

Balmes et al. (1987) studied the relationship between duration and concentration of SO_2 exposure and bronchoconstriction in male and female adult asthmatics. The subjects were exposed to 0.5 or 1 ppm SO_2 for 1, 3 and 5 minutes. Of the eight subjects, two developed substantial chest tightness after inhalation of 1 ppm for 1 minute. Seven of the eight subjects developed wheezing and chest tightness after inhaling 0.5 ppm for 3 and 5 minutes (Study ID ◆ 064).
Hackney et al. (1984) exposed young adult asthmatics to 0.75 ppm SO_2 for three hours. The subjects vigorously exercised for the first 10 minutes of exposure and rested for the balance of the exposure time. General asthmatic symptoms were increased post-exercise relative to pre-exposure levels, but these effects had returned to pre-exposure levels by one hour post-exercise (Study ID ◆ 079).
Koenig et al. (1981) exposed asthmatic adolescent subjects to 1 ppm SO_2 for 30 minutes at rest and 10 minutes during exercise. Three subjects reported shortness of breath and five reported wheezing (Study ID ◆ 041).
Roger et al. (1985) exposed young asthmatic male subjects to levels of SO_2 of 1 ppm for 75 minutes/week for 4 weeks. The subjects reported shortness of breath and chest discomfort after 10 minutes of exposure to 1 ppm. A trend towards increased wheezing, deep breathing discomfort, and cough was also observed (Study ID ● 087).

Effects observed-healthy and asthmatic subjects
Witek et al. (1985) investigated subjective responses to concentrations of SO_2 less than 1 ppm for 40 minutes in healthy and asthmatic subjects. Asthmatics reported chest tightness, wheezing, dyspnea and cough, while the healthy subjects reported taste and odour complaints. There was an increase in the number and severity of the complaints associated with increasing concentration (Study ID ◆ 093).

No effects observed
Bailey et al. (1982) exposed twenty-four young asthmatic adults to 0, 0.25, and 0.5 ppm SO_2 for one hour. No significant symptoms were observed after exposure (Study ID ▲ 075).
Kagawa (1983) observed no symptoms in seven healthy male subjects exposed to 0.15 ppm SO_2 for 2 hours (Study ID ◆ 072).
Linn et al. (1985b) exposed twenty-four adult subjects with chronic obstructive pulmonary disease to 0, 0.4 and 0.8 ppm SO_2 for 1 hour. There were no significant changes in symptom reporting between the pre- and postexposure periods (Study ID ◆ 101).

Eye symptoms
Douglas and Coe (1987) applied concentrations of SO_2 ranging from 3 to 60 ppm SO_2 to the eyes of subjects for

15 seconds using goggles and to the lungs for 10 breaths, via a mouthpiece. These exposure conditions, particularly for the eyes, were quite extreme. Observed eye response included a dose-dependent increase in tear production with exposure, which returned to baseline within 15 minutes post-exposure. The threshold concentrations at which symptoms were first seen or reported were observed. The threshold concentration for eye effects was observed to be 5 ppm, while that for the lung was 1 ppm (Study ID ● 121).

Non-clinical studies

Haider et al. (1981) exposed guinea pigs to 10 ppm SO_2 for 1 hour/day for 21 days to observe any changes in brain lipid chemistry. They observed signs of nasopharyngitis, somnolence, staggering, itching, preening, and skin and eye-irritation (Study ID ▲ 159).

Johnson et al. (1972) exposed male mice to 40 ppm SO_2 for 4 to 11 days and observed depressed feed and water intake, depressed body weight and O_2 consumption, and upper respiratory damages upon initial exposure. Immediately upon cessation of exposure, recovery of body weight began and O_2 consumption was normal by 32 to 34 days post-exposure (Study ID ◆ 261).

Matsumura (1970a, 1970b) exposed guinea pigs to 20, 60, 180 and 300 ppm SO_2 for 30 minutes in one experiment (Study ID ● 142) and 400 ppm for 30 minutes in another (Study ID ● 143). No signs of irritation were seen at concentrations lower than 300 ppm.

Epidemiology studies

Donoghue and Thomas (1999) examined the relationship between atmospheric SO_2 concentrations and hospital presentation for asthma in a town in which both a copper smelter and a lead smelter are major producers of SO_2. Over a three-year period, they observed no association between peak SO_2 concentrations up to 3300 ppb and hospital presentations or admissions for asthma, wheeze, or shortness of breath (Study ID ◆ 007).

Cohen et al. (1974) conducted a telephone survey of irritative symptoms during publicized and unpublicized elevated air pollution events and during a time of low air pollution. They observed increases in reported eye and throat irritation, chest discomfort, shortness of breath, restricted activity, and medical visits in adults during the two high pollution episodes compared to the low pollution time period. Atmospheric SO_2 concentrations were measured at between 0.01 and 0.15 ppm (Study ID ◆ 011).

Several studies investigated general hospital admissions or school absences without specific health outcomes. Xu et al. (1995a,b) conducted a time-series analysis of daily hospital visits and air pollution data. A 38 ppb increase in SO_2 was associated with internal medicine and pediatric outpatient visits, and emergency room visits. SO_2 was found to be a highly significant predictor of total and nonsurgery outpatient visits. Information on monitoring station location was not reported. In addition, only patients able to pay the registration fee would go to the hospital, suggesting some bias is likely (Study ID ● 424, 474).

Park et al. (2002) found that exposure to SO_2 in the range of 2.68 to 28.11 ppb) was associated with illness-related absences from school among elementary school students. The specific type of illness was not reported. There was also

a significant protective association between SO_2 and non-illness related absences. Again, specific reasons for these absences were not recorded. The teachers determined whether the absences were related to illness or not for the purposes of the study (Study ID ● 429).

Case reports

Several case reports of accidental exposure to very high levels of SO_2 by fewer than 10 individuals have been reported. Rabinovitch et al. (1989) presented a two-year follow-up of two miners who had been exposed to high concentrations of SO_2 after a mine explosion. Among various airway effects, the individuals reported markedly reduced exercise tolerance (Study ID ◆ 272).

Harkonen et al. (1983) report on a four-year follow-up of seven men who were accidentally exposed to SO_2 in a pyrite dust explosion. Immediately following these high levels of exposure, the men exhibited thoracic pain, coughing, conjunctival irritation and in some cases, corneal erosion (Study ID ● 021).

Galea (1964) reported a case of a 35-year old man who accidentally inhaled high levels of SO_2. Ten days after exposure the patient reported dry, irritable, tiresome cough, dyspnea, and copious amounts of mucus (Study ID ● 271).

Woodford et al. (1979) describe the case of a previously healthy young man who reported symptoms of burning and tearing eyes, rhinorrhea, cough and almost passing out after a brief exposure to a high concentration of SO_2 (Study ID ● 269).

Charan et al. (1979) reported the symptoms of three survivors of an industrial accident in which five men were exposed to high concentrations of SO_2. The three survivors reported irritation and soreness of the eyes, nose, and throat, tightness in the chest, and intense dyspnea. An eye examination showed severe conjunctivitis and superficial corneal burns (Study ID ● 270).

Summary

Clinical

Several studies reported signs and symptoms as observations concurrent to investigation of other effects. Healthy subjects reported nose and throat irritation, taste and odour complaints, and discomfort during single exposures (15 and 28 ppm for 10 minutes or to less than 1 ppm for 40 minutes) as well as during multiple exposures (1 ppm for 4 hours/day, 3 days/week for 3 weeks and 1 to 25 ppm for 6 hours/day for 3 consecutive days). Some coughing was observed in the healthy subjects during forced mouth breathing. Asthmatic subjects reported chest tightness, shortness of breath, wheezing, asthma symptoms, dyspnea and cough during single exposure both with and without exercise. Concentrations ranged from 0.5 to 1 ppm and lasted between 3 minutes and 3 hours. No symptoms were reported in asthmatics after exposure to 0.5 ppm for one hour, subjects with COPD exposed to 0.8 ppm for one hour, or healthy subjects exposed to 0.15 ppm for 2 hours.

Non-clinical

Few non-clinical studies reported irritative symptoms as a result of SO_2 exposure. Itching, preening, somnolence, and eye- irritation were observed in guinea pigs exposed to 10 ppm for 1 hour/day for 21 days. Depressed feed

and water intake and decreased body weight and oxygen consumption were observed in male mice exposed to 40 ppm for 4 to 11 days. Recovery of body weight and oxygen consumption began immediately after cessation of exposure.

Epidemiology

Shortcomings in epidemiology studies and case-reports have been detailed in the mortality and respiratory summaries of this report. The same limitations apply to the few moderate epidemiology studies and case-reports reporting general signs and symptoms. Responders in a telephone survey during elevated air pollution events with ambient SO_2 levels up to 0.15 ppm reported increased eye and throat irritation, chest discomfort, shortness of breath, and restricted activity. Two miners exposed to very high concentrations in a mine explosion reported reduced exercise tolerance two years after the accident. No association was reported between ambient SO_2 concentrations up to 3.3 ppm and hospital admissions for asthma, wheeze, or shortness of breath.

G. Cardiovascular System

Non-clinical studies were most numerous, although clinical and epidemiology studies were also available. However, many of the studies were judged to be of questionable quality and the information obtained not very reliable or relevant.

Clinical studies

Only two clinical studies dealt with cardiovascular effects. Tunnicliffe et al. (2001) exposed 12 normal and 12 asthmatic male and female adult humans to 200 ppb SO_2 (to mimic likely air pollution levels) for 1 hour and recorded the electrocardiograms. No significant differences in maximum or minimum heart rates were seen in either group. In normal subjects, total power, high frequency power and low frequency power appeared higher with SO_2 exposure. These indices appeared lower in the asthmatic group upon SO_2 exposure. However, the only statistically significant result was the difference in total power found in air *vs.* SO_2 in normal subjects. This lone result is weak evidence for the authors' conclusion that "SO_2 exposures at concentrations which are frequently encountered during air pollution episodes can influence the autonomic nervous system" (Study ID ◆ 071).

Amdur et al. (1953) observed no statistically significant effects on pulse-rate in subjects exposed to 1 to 8 ppm SO_2 for 10 minutes (Study ID ● 032).

Non-clinical studies

Several studies investigated changes in heart rate with SO_2 exposure. A single high quality study found no differences in heart rate or blood pressure in chickens exposed to 100 ppm SO_2 for 1 hour (Fedde and Kuhlmann, 1979). A statistically significant increase in heart rate was observed upon exposure to 5000 ppm for one hour. Most of the chickens exposed at this level died (Study ID ▲ 183).

Wang et al. (1996) observed a mild decrease in heart rate in Sprague-Dawley rats with exposure for two tidal breaths to air containing 5000 ppm SO_2. This decrease lasted for 3 to 8 breaths before returning to control levels. No increase in blood pressure was observed (Study ID ◆ 211).

Callanan et al. (1974) observed an increase in blood pressure and heart rate in geese after inhalation of 100 to 400 ppm of SO_2 for 1 to 3 minutes. The same

study found striking differences between geese and mammals in terms of response to inhaled SO_2 (Study ID ◆ 233).
Drew et al. (1983) exposed two lines of Dahl rats to SO_2 at 50 ppm for 6 hours per day, 5 days a week for 6 weeks. One line of rats was resistant to salt-induced hypertension; the other was not. In the rats resistant to hypertension, a slight but consistent decrease in blood pressure was observed with exposure to SO_2. In the rats not resistant to hypertension, an increase in blood pressure was observed in the SO_2-exposed animals versus the air-exposed animals. These observations disappeared after the last SO_2 exposure (Study ID ● 241).

Langley-Evans et al. (1996) observed depleted glutathione levels in the hearts of rats exposed to levels of SO_2 as low as 5 ppm and as high as 100 ppm for 5 hours/day, for 7 to 28 days (Study ID ◆ 251).
Haider (1985) observed elevated levels of cholesterol, total lipids and phospholipids in guinea pig hearts and decreased concentration of gangliosides after exposure to 10 ppm for 1 hour a day for 30 days (Study ID ◆ 163).
Rana et al. (1979) observed decreased lipid levels and increased moisture content in squirrel hearts after exposure to 500 ppm SO_2 for 4 minutes (Study ID ● 147).
Balchum et al. (1960) observed a low, uniform concentration of $^{35}SO_2$ in the heart muscle of dogs after inhalation of 1.8 to 148 ppm $^{35}SO_2$ for 30 to 40 minutes (Study ID ● 237).

Epidemiology studies
Wong et al. (2002) reported significant positive associations of similar size between an incremental 4 ppb increase of SO_2 (baseline concentrations 6.8±4.7 ppb) and daily admissions for cardiac diseases in Hong Kong and London, England. No information is reported on the number of monitoring stations and their location (Study ID ◆ 423).
Sunyer et al. (2002) observed a significant increase in daily numbers of all cardiovascular admissions except stroke and particularly ischemic heart disease with a same-day increased in daily SO_2 concentrations (range: 1.9-8 ppb). However, not all cities involved in this study were able to provide complete exposure and outcome data. Confounding factors were not considered (Study ID ● 459).
Morris et al. (1995) reported inconsistent results for the association between an increase of 0.05 ppm SO_2 and hospital admissions for congestive heart failure. Only two of seven US cities had statistically significant associations: New York with the highest average SO_2 levels, and Los Angeles with the lowest. The results and discussion section focus on CO. There is limited information on monitoring and many confounding factors (Study ID ● 387).

No association observed
In a study on the effects of atmospheric SO_2 pollution on mortality, Derriennic et al. (1989) compared the populations of two French cities with average SO_2 concentrations of 25 and 19 ppb. No statistical association was found between SO_2 pollution and cardiovascular deaths. However, because of the difficulties of measuring SO_2 exposure and the potential for misclassification of cause of death, these results are inconclusive (Study ID ● 002).
Ponka and Virtanen (1996a) reported no significant associations between SO_2 (range: 0.08-36 ppb) and hospital admissions for ischemic cardiac and

cerebrovascular diseases. Regression results for SO_2 are not reported. Some confounding factors were considered (Study ID ● 388).
Peters et al. (2000) reported no association between implanted cardioverter defibrillator discharges and SO_2 concentrations (mean 0.007 ppm) in Massachusetts. Defibrillator discharge was used a s a surrogate measure for cardiac arrhythmia. Exposure assessment was a weakness as only one monitor collected data for a large area of eastern Massachusetts. Statistical significance was not reported (Study ID ● 441).

Summary:

Clinical studies:
Only one moderate quality study was identified as investigating cardiovascular effects. This study reported weak evidence of a difference in total power recorded in an electrocardiogram after exposure to 0.2 ppm for 1 hour.

Non-clinical studies:
A high quality study reported an increase in the heart rate of chickens with exposure to 5000 ppm for 1 hour, but no effect on heart rate or blood pressure at exposure to 100 ppm for 1 hour. Two moderate studies also investigated effects on heart rate and blood pressure. Rats exhibited decreased heart rate after two tidal breaths of 5000 ppm. Geese exhibited increased blood pressure and heart rate with 1 to 3 minutes of exposure to 100 to 400 ppm. Multiple exposure designs identified decreased glutathione in the hearts of rats (5 to 100 ppm for 5 hours a day for 28 days) and an increase in cholesterol, total lipids, and phospholipids in guinea pig hearts (10 ppm for 1 hour/day for 30 days). The clinical significant of these results is unclear.

Epidemiology studies:
In the lone moderate study in this category, a small but significant association was reported between daily admission for cardiac disease in London England and Hong Kong and an incremental increase of 4 ppb in ambient SO_2 concentrations (baseline concentrations 6.8±4.7 ppb). The limitations previously identified for epidemiology studies apply to this study. In particular, exposure assessment was a major limitation and the study was rated "moderate-to-low".

H. Eye

Clinical studies
In an investigation of the effects of SO_2 and respirable carbon aerosol on 20 healthy, non-smoking adult subjects, Kulle et al. (1986) observed no adverse effects on the eye with exposure to 1 ppm SO_2 alone, 4 hours per day, 3 days per week for 3 weeks (Study ID ▲ 096).
Two studies observed increases in tear production with exposure to SO_2. Coe and Douglas (1982) exposed six subjects to 50 ppm SO_2 for 5 minutes. None of the subjects reported subjective sensations of eye irritation during or after this exposure period (Study ID ● 065).
In contrast, Douglas and Coe (1987) exposed subjects to levels of SO_2 varying from 3 to 60 ppm for 15 seconds. The threshold for tear production was found to be 5 ppm (Study ID ● 121).

Non-clinical studies
Only one non-clinical study reported any effects of SO_2 exposure on the eyes

(Haider et al., 1981). In this study eye effects were not the main focus and are mentioned briefly amongst other signs and symptoms of SO_2 exposure as follows: "exposure to guinea pigs to SO_2 lead to signs of....eye irritation...". Guinea pigs were exposed to 10 ppm, one hour per day for 21 days (Study ID ▲ 159).

Epidemiology studies

Cohen et al. (1974) carried out a telephone survey to investigate the reporting of irritative symptoms during well-publicized and unpublicized periods of moderately elevated air pollution and a period of low pollution. Peak hourly SO_2 concentrations ranged between 0.01 and 0.15 ppm for the low and elevated pollution events. Significant increases in eye irritation were observed during both elevated pollution episodes compared to the control (low pollution) period. There was no difference in the reporting of eye irritation between the publicized and unpublicized episodes (Study ID ◆ 011).

Complaints of irritative effects prompted a Health Hazard Evaluation of Portland Cement plants to assess whether SO_2 exposure was the genesis of the problems (NIOSH, 1984). SO_2 levels at the plants were measured to be 0.2 to 1.8 ppm. The question of whether SO_2 exposure caused the eye irritation was undetermined (Study ID ● 267).

Harkonen et al. (1983) followed 7 men unintentionally exposed to "high levels" of SO_2 for 20 to 45 minutes during an explosion in a pyrite mine. The levels of SO_2 exposure were not determined. Immediately after exposure, conjunctival irritation in all cases and corneal erosion in some cases were observed (Study ID ● 021).

Woodford et al. (1979) describe the case of a healthy young man accidentally exposed to a high concentration of SO_2 for 15 to 20 minutes. The actual SO_2 concentration was not determined. The subject reported symptoms of burning and tearing eyes after exposure. (Study ID ● 269).

These last two studies are of limited use in determining the effects of low dose exposure to SO_2, being case-reports rather than epidemiologic or clinical studies. In addition, SO_2 exposure concentrations were not measured. In all epidemiology studies, the issue of SO_2 exposure determination is not well addressed.

Summary:

SO_2 is generally acknowledged to have irritant effects on the eye. However, very few studies fitting the criteria for this report (e.g. peer-reviewed, scientific literature) report eye effects and none of the studies reviewed specifically investigated eye effects. Some studies with a focus on other health endpoints reported eye effects as a peripheral observation.

Clinical studies:

Of the three studies reporting eye effects, one was rated of high quality while the other two were low quality. The high quality study reported no adverse effects on the eye with exposure to 1 ppm for 4 hours/day, 3 days/week for 3 weeks.

Non-clinical studies:

The single non-clinical study reporting eye effects was ranked high quality. Eye effects were not a major focus of this study. However, the study reports that exposure of guinea pigs to 10 ppm for 1 hour/day for 12 days leads to signs of eye irritation.

Epidemiology studies:
Only one of four epidemiology studies mentioning eye effects was ranked moderate quality. This study reported that increases in eye irritation were observed during elevated pollution events with ambient levels up to 0.15 ppm.

I. Gastrointestinal System

No studies clinical or epidemiology were found that investigated or reported effects to the gastrointestinal system as a result of acute SO_2 exposure.

Non-clinical studies

Meng et al. (2003) suggest that inhalation of SO_2 (8.4±0.8, 21±1, and 43±3 ppm) increased levels of lipid peroxidation in stomachs and intestines of male and female Kunming albino mice. These results suggest a toxicological role of SO_2 inhalation on these organs in mice. Confidence intervals were not reported, but Good Laboratory Practice guidelines were generally followed (Study ID ◆ 460).

J. General Biochemical Effects

There is slight human and animal evidence for the potential to use SO_2 metabolites as a possible biomarker of exposure to SO_2. There is also some evidence of various other biochemical effects. However, the clinical relevance of these effects is unclear. The confidence level of many of the studies was low, limiting the reliability and utility of the results.

Clinical studies

Trenga et al. (1999) tested 47 adult asthmatics for characteristics associated with SO_2 sensitivity. They found correlations between plasma beta-carotene concentrations and peak expiratory flow values, ascorbate concentrations and baseline pulmonary function indices, as well as with high-density lipoprotein concentrations and forced expiratory flow values. There were no correlations between plasma antioxidant nutrient concentrations and sensitivity to inhaled SO_2 (Study ID ◆ 055).

Kienast et al. (1994b) reported a dose-dependent stimulation of reactive oxygen intermediates (ROI) after 30 and 60 minutes of exposure to SO_2 at levels of 0.3 to 1.5 ppm. However, the study authors report that there is no conclusive evidence as to the measured amount of ROI that is sufficient to induce clinically relevant pulmonary fibrosis, so the clinical significance of these findings is uncertain (Study ID ◆ 312).

Gunnison and Palmes (1974) investigated the possible production of S-sulfonate in human plasma as a function of exposure to SO_2. After subjecting humans to controlled SO_2 exposures of 0, 0.3, 1, 3, and 6 ppm continuously for up to 120 hours, they determined that plasma levels of S-sulfonate showed a positive correlation with atmospheric sulfur dioxide. However, the weaknesses of this study limit confidence in the results. Little detail was available on the characteristics of the study volunteers, the monitoring methods, and the method of exposure (Study ID ● 112).

Grote and Thews (1973) observed that the amount of SO_2 that can dissolve in human blood with base excess values between +10 and –15 mEq/L and normal

hemoglobin increases with increasing blood O_2 or CO_2 and decreasing blood pH. The experimental detail was lacking in terms of SO_2 exposure delivery and dose measurement. Recruitment methods and characteristics of the volunteers such as age and pre-trial health were not reported (Study ID ● 265).

Yokoyama et al. (1971) reported that whole blood levels of $^{35}SO_2$ rose steadily with exposure to 50 ppm. The exposure duration was not clearly stated in the study, nor are many important experimental details included in the report. The clinical and toxicological significance of these results are unclear (Study ID ● 373).

Non-clinical studies

Guinea pigs

Etlik et al. (1995) found higher methemoglobin and sulfhemoglobin, as well as lipoperoxidation and osmotic fragility in guinea pigs exposed to 10 ppm SO_2 by inhalation for 1 hour per day for 30 days (Study ID ◆ 236).

Matsumura (1970) observed hemaglutination in five of ten guinea pigs exposed to 330 ppm SO_2 by inhalation for 30 minutes. Age and sec of animals were not specified which is a consideration when only one half of the animals displayed a response (Study ID ● 142).

In a general exploration of the biological effects of SO_2 exposures on guinea pigs, Lee and Danner (1966) observed increased hemoglobin at all concentrations between 6 and 310 ppm and blood inorganic sulfur concentrations above 19 ppm for a 60-minute exposure. Strain, sex, and pre-trial health, feed and test conditions were not reported. There was a single animal for each dose and statistical significance was not reported (Study ID ● 254).

Rats

Lovati et al. (1996) investigated the effects of SO_2 exposure on serum lipids/lipoproteins and on glucose metabolism in rat models of hypercholesterolemia and diabetes. In normal animals fed either a standard or a cholesterol-enriched diet, they observed a dose-dependent increase in plasma triglycerides and a significant reduction in HDL cholesterol levels. A reduction of plasma triglycerides and an increase in plasma HDL cholesterol was observed in diabetic animals upon exposure to 5 or 10 ppm SO_2 continuously for 15 days (Study ID ▲ 152).

Jonek et al. (1976) traced the uptake of SO_2 into the bodies of Wistar rats. Rats were exposed to $^{35}SO_2$ in air by inhalation. The highest radioactivity in blood serum was observed 2 hours after exposure. The radioactivity was still high 24 hours after exposure, but decreased in the following days (Study ID ◆ 151).

Baskurt (1988) exposed male Swiss albino rats to 0.87 ppm SO_2 for 24 hours and observed higher hematocrit and sulfhemoglobin values in the exposed animals compared to the controls. They observed that whole blood and packed cell viscosities were lower in the rats exposed to SO_2 than in the controls. There were no differences in the plasma viscosities between exposed and control animals (Study ID ◆ 192).

Azoulay et al. (1980) found no differences in blood variables or hemoglobin affinity in rats exposed to 2 ppm SO_2 continuously for 1 to 49 days compared to control animals for 1 hour/day for 30 days (Study ID ◆ 225).

Gause and Barker (1978) investigated the uptake of SO_2 in the Sprague-

Dawley rat during exposures of 5 to 20 ppm continuously for 7 days and observed that approximately 10% of the SO_2 inhaled is found in the plasma or serum within the first 30 minutes of exposure. Exposure assessment was not well defined and information on the experimental protocol is lacking (Study ID ● 193).

Baskurt et al. (1990) observed no significant differences between the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC between control rats and rats treated with 1 ppm SO_2. Erythrocyte deformability indexes of the SO_2 treated animals were significantly higher than controls. However, Good Laboratory Practice guidelines were not followed in this study, which has substantial weaknesses in design and reporting (Study ID ● 302).

Mice

Vanjonack and Johnson (1974) exposed mice to 40 ppm SO_2 for times between 0.5 and 24 hours and observed a statistically significant time-dependent decrease in plasma thyroxine levels at exposure times of 12 and 24 hours. There was also a statistically significant time-dependent increase in plasma glucocorticoids at 1 and 12 hours (Study ID ◆ 212).

Meng et al. (2002) observed increased frequencies of polychromatic erythrocyte micronuclei formation (MNPCE) in mouse bone marrow with increased doses of SO_2 from 5 to 32 ppm. The authors state that these are preliminary results and clinical significance is unclear although the study authors suggest that SO_2 may be a clastogenic and genotoxic agent in mice (Study ID ● 380).

Rabbits

Gunnison and Benton (1971) did not detect free sulfite in the plasma of rabbits immediately following exposure to 23.5 ppm SO_2 continuously for 14 or 62 hours. However, elevated levels of plasma and serum S-sulfonate were observed. Animal characteristics and treatment were not specified, nor were pre-test and acclimation conditions (Study ID ● 222).

Chickens

Fedde and Kuhlman (1978) exposed male chickens to concentrations of SO_2 up to 5000 ppm for 60 minutes by inhalation, either through tracheal cannulae or with intact respiratory systems. They observed no changes in arterial blood gases and pH at 100 ppm; however, there were statistically significant decreases in blood pH and increases in blood CO_2 at 5000 ppm with both methods of inhalation. In addition, statistically significant decreases in blood O_2 were observed in those birds with intact respiratory systems (Study ID ▲ 183).

Epidemiology studies

No epidemiology studies investigated this outcome for SO_2 exposure, specifically.

Summary:

Clinical

Two moderate quality studies were identified. In one study, no association was observed between plasma antioxidant nutrient concentrations and sensitivity to inhaled SO_2. In the other study, a dose-dependent stimulus of

reactive oxygen intermediate (ROI) was reported with exposure to concentrations between 0.3 and 1.5 ppm for 30 to 60 minutes. However, it is unclear how much ROI stimulation is required to induce clinically relevant pulmonary fibrosis.

Non-clinical

Two high quality studies were identified. One investigated the effects of SO2 exposure on serum lipids and lipoproteins and glucose metabolism in diabetic and normal rats. With continuous exposures of 5 and 10 ppm for 15 days, increases in plasma triglycerides and decreases in plasma HDL cholesterol were reported in the healthy rats. Increases in plasma triglycerides and increases in plasma HDL cholesterol were reported in the diabetic rats. The other high quality study investigated responses of chickens to high levels of SO_2 (5000 ppm for 1 hour). Decreased blood pH and increased blood CO_2 were observed. Moderate studies reported increased sulfhemoglobin values, and lower whole blood and packed cell viscosity, but no differences in plasma viscosity (0.87 ppm for 24 hours in rats), and a time-dependent decrease in plasma thyroxine levels in mice exposed to 40 ppm for 12 to 24 hours. One study reported no differences in blood variables or hemoglobin affinity in rats exposed to 2 ppm continuously for 1 to 49 days.

Epidemiology

No epidemiology studies were identified that fit the criteria for inclusion.

K. Immunological System

There is some evidence that SO_2 influences the immunological system. Various effects and potential mechanisms of action have been investigated, making verification of effects and identification of SO_2 concentrations difficult.

Clinical Studies

Winterton et al. (2001) exposed asthmatic subjects to 0.5 ppm SO_2 for 10 minutes and analyzed buccal cell samples for genetic polymorphisms. They found that increased response to SO_2 was associated with wild-type allele of the TNF-alpha promoter polymorphism, but not with other polymorphisms. They concluded that the mechanisms of asthmatic sensitivity may be associated with this wild-type allele (Study ID ◆ 035).

Anderson et al. (1977) experimentally induced rhinovirus infection in two groups of subjects. One group was exposed to SO_2 at 5 ppm for 4 hours while the other group (controls) was exposed to pollution-free air under the same conditions. There was no difference in the number of subjects who developed colds, but there was a 50% decrease in nasal mucus flow rate in the SO_2-exposed group compared to the control group. The SO_2-exposed group also had fewer symptoms and less but more persistent virus shedding than the control group. There were no differences in antibody response between the two groups (Study ID ◆ 048).

Sandstrom et al. (1989) used bronchoalveolar lavage to investigate the effect of SO_2 on the human lung. Twenty-four hours after exposure to 4 ppm SO_2 for 20 minutes, there was an increase in alveolar macrophage activity. Twenty-four hours after exposure to 8 ppm SO_2 for 20 minutes, a greater increase in alveolar macrophage activity was observed. Seventy-two hours after

exposure, activity had returned to pre-exposure levels (Study ID ◆ 083).
Sandstrom et al. (1989) performed bronchoalveolar lavage on eight subjects 4, 8, 24 and 72 hours after exposure to 4, 5, 8, or 11 ppm SO_2 for 20 minutes. They found a significant increase in lysozyme positive and alveolar macrophages/monocytes at all concentrations. After exposure to 8 and 11 ppm SO_2, the total number of alveolar macrophages/monocytes was significantly increased. Increases in the total number of mast cells were seen 24 hours after exposure to 5 ppm SO_2 and above (Study ID ● 091).
Koenig et al. (1987) investigated the effect of albuterol in preventing SO_2-induced bronchoconstriction. Their results suggest that the mechanism of action for SO_2-induced bronchoconstriction involves mast cell degranulation or the adrenergic nervous system (Study ID ◆ 103).
Sheppard et al. (1981a) investigated the mechanism of action of SO_2 by exposing asthmatic subjects to 0.5 or 1.0 ppm SO_2 and cromolyn or lactose for 10 minutes while exercising. Their results suggest that SO_2 may induce bronchoconstriction by stimulating the release of mediators from mast cells (Study ID ● 058).

Non-clinical studies
Azoulay-Depuis et al. (1982) investigated the effect of SO_2 exposure on resistance to respiratory infection by exposing female mice to 10 ppm SO_2 for up to 3 weeks. There was a significant increase in mortality in the groups of mice exposed to SO_2 for 7 or more days compared to controls. There was a decrease in mean survival time for mice exposed to all levels of SO_2 (Study ID ▲ 172).
Ukai (1977) investigated the effect of exposure to low levels (0.03 to 0.1 ppm) of SO_2 on the pathogenesis of influenza virus infection in mice. In mice exposed to both SO_2 and the virus, antibodies to the virus developed more rapidly than in those mice exposed to virus alone. In addition, mice exposed to SO_2 but not the virus showed an increase in the number of goblet cells in nasal epithelial cells. These observations suggest that SO_2 alters the nasal mucus membranes, eliminating a major defensive barrier against disease and subsequently resulting in increased severity of influenza infection (Study ID ◆ 207).
Fairchild (1977) investigated the effects of SO_2 on the growth of influenza virus in the nasal epithelia of mice. Exposure to 6 ppm SO_2 for 7 days caused partial inhibition of influenza virus growth in the nasal epithelium and no propagation in the lungs (Study ID ◆ 238).
Trimpe et al. (1986) observed that there was no difference in the rate of clearance of Listeria monocytogenes bacteria from hamsters after exposure to 27 ppm SO_2. Time of SO_2 exposure, either prior to or simultaneous to bacteria exposure, did not affect the clearance rates (Study ID ● 134).

Park et al. (2001) found that repeated exposure to low levels of SO_2 (0.1 ppm) might enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs (Study ID ▲ 259).
Riedel et al. (1988) investigated the effect of SO_2 exposure on bronchial sensitization to inhaled antigens in the guinea pig. After exposing the animals to 0.1-16.6 ppm for 8 hours/day for 5 days, they observed a significant increase in ovalbumin-specific antibodies in serum and bronchoalveolar

fluid in SO_2-exposed groups compared to controls (Study ID ◆ 133).

Gause and Rowlands (1975) observed a dose-dependent spectral change in labeled human lymphocyte membranes after exposure to inhaled SO_2. They speculate that the changes may indicate the formation of microparticles or microaggregates of membrane protein structures (Study ID ● 201).

Watson and Brain (1980) investigated the extent of particle uptake in normal and SO_2-damaged airway epithelia in mice. They observed that exposure to SO_2 at 250 ppm for 3 hours increased the uptake of iron in airway epithelium (Study ID ◆ 209).
Okuyama et al (1979) observed an increase in the number of macrophages, lymphocytes, plasma cells and neutrophils in the epithelium and lamina propria of chickens exposed to 3.4 to 18.5 ppm for 1 to 14 days (Study ID ● 199).
Norris and Jackson (1989) observed increased response to aerosolized histamine as a result of exposure to 200 ppm SO_2 for 2 hours in dogs. In addition, there was an increase in airway permeability to plasma proteins and an increase in epithelial cell shedding (Study ID ● 146).

Epidemiology studies
In the only epidemiology study in this section, Boezen et al. (1999) investigated factors that could increase children's susceptibility to air pollution. They found that children with bronchial hyperresponsiveness and with high serum concentrations of total IgE (>60 kU/L) were particularly susceptible to air pollution, but not SO_2, specifically (Study ID ◆ 005).

Summary

Clinical
Several studies investigated the mechanisms of action of SO_2 on immunological system functions. Increased alveolar macrophage activity was reported in subjects exposed to 4 and 8 ppm for 20 minutes. One study induced rhinovirus infection in an SO_2-exposed group (5 ppm for 4 hours) and a control group. The number of subjects who developed colds was not different between the two groups. However, the SO_2-exposed group experienced a decrease in nasal mucus flow rate, fewer symptoms, and less but more persistent virus shedding. It has been suggested that mechanisms of asthmatic sensitivity may be associated with a wild-type allele of the TNF-alpha promoter polymorphism or may involve mast cell degranulation.

Non-clinical
Increased mortality and decreased survival time was observed in a group of female mice with respiratory infection exposed to 10 ppm for up to 3 weeks compared to non-exposed controls. Mice exposed to 0.03 to 0.1 ppm and an influenza virus developed antibodies to the virus more rapidly than mice exposed to the virus alone. The literature suggests that SO_2 alters nasal mucus membranes thereby decreasing a defensive barrier to disease and resulting in increased severity of influenza infection. However, another study reported that exposure to 6 ppm for 7 days caused partial inhibition of influenza virus growth in the nasal epithelium and no propagation in the lungs. Studies on guinea pigs suggested

that exposure to low levels of SO_2 (1ppm) might enhance the development of ovalbumin-induced asthmatic reactions and reported a significant increase in ovalbumin-specific antibodies in serum and bronchoalveolar fluid with exposure to 0.1 to 16.6 ppm for 8 hours/day for 5 days. A study on mice exposed to 250 ppm for 3 hours reported an increased uptake of iron in airway epithelium. The clinical significance of many of these studies is unclear and not discussed in the studies themselves.

Epidemiology

One moderate epidemiology study reported that children with bronchial responsiveness and high serum concentrations of total IgE were particularly susceptible to air pollution, but not SO_2 specifically.

L. Kidney and Liver

Clinical studies

No clinical or epidemiology studies were found that investigated or reported liver or kidney health outcomes.

Non-clinical studies

Lovati et al. (1996) observed a dose-related increase in liver weight and an increase of triglycerides in the livers of rats on a standard diet after exposure to 10 ppm SO_2 continuously for 15 days. Diabetic rats showed a decrease in liver weight after exposure to both 5 and 10 ppm SO_2, as well as a dose-dependent decrease in liver triglycerides (Study ID ▲ 152).

Haider (1985) observed depletion of phospholipids, cholesterol and cholesterol/phospholipid ratios (C/P ratios) and decreased lipid peroxidation in guinea pig livers and kidneys after exposure to 10 ppm SO_2 for 1 hour per day for 30 days (Study ID ◆ 163).

Langley-Evans et al. (1996) investigated the detoxification of SO_2 in rats exposed to concentrations from 5 to 100 ppm for 5 hours/day for 7 to 28 days. They observed depleted glutathione levels in the liver and kidney at all concentrations. Glutathione reductase activity was decreased in the liver at 5 ppm. At 50 ppm glutathione S-transferase activity was unaltered in the liver, suggesting an impairment of the sulfitolysis reaction (Study ID ◆ 251).

Balchum et al. (1960) investigated the uptake and distribution of $^{35}SO_2$ in dogs. After inhalation of 1.8 to 148 ppm for 30 to 40 minutes, they observed the highest S^{35} concentration in the trachea, lungs, and lymph nodes with the next highest concentration in the kidneys. A low but uniform concentration was observed in the liver (Study ID ● 237).

Summary:

No clinical or epidemiology studies investigating or reporting liver or kidney effects and fitting the criteria were identified for this review.

Non-clinical

Increases in liver weight and triglycerides in the livers of healthy rats exposed to 10 ppm continuously for 15 days were observed in a high quality study. The same study reported decreased liver weight and a dose-dependent decrease in liver triglycerides in diabetic rats after exposure to 5 or 10 ppm continuously for 15 days. Depletion of phospholipids, cholesterol, cholesterol/phospholipid ratios and lipid peroxidation in guinea pig livers was reported after exposure to 10 ppm for 1 hour/day for 30 days. Glutathione

reductase activity was decreased in rat livers at 5 ppm for 5 hours/day for 7 to 28 days. In addition, glutathione levels in the liver and kidney were reduced at concentrations between 5 and 100 ppm for the same exposure protocol.

M. Metabolic Systems

Clinical

There were no clinical or epidemiology studies investigating the metabolic effect of SO_2 exposure.

Non-Clinical

Johnson et al. (1972) found that continuous exposure of mice to 40 ppm SO_2 for 4 to 11 days depressed metabolism as measured by O_2 consumption. Oxygen consumption returned to normal by 32 to 34 days post-exposure (Study ID ◆ 261).

Meng (2003) reported a statistically significant decrease in Cu, Zn-superoxide dismutase in the brain, lung, stomach, and intestine of male mice and in the lung, heart, liver intestine and kidney in female mice after exposure to 20 ppm SO_2 for 6 hours a day for 7 days. Significantly decreased activities of Se-dependent glutathione peroxidase were observed in all organs of mice of both sexes and a significant decrease of catalase activity in livers from both sexes of mice. The clinical significance was not clear (Study ID ◆ 381).

Langley-Evans et al. (1996) observed varied levels of glutathione, as well as varied enzyme activity in the lung, liver, heart and kidney of Wistar rats exposed to levels of SO_2 between 5 and 100 ppm for 5 hours/day for 7 to 28 days. They concluded that SO_2 is a potential glutathione-depleting agent (Study ID ◆ 251).

Leung et al. (1985) found that glutathione S-sulfonate, a metabolite of SO_2 in the body, acts as an inhibitor of glutathione S-transferase in rat livers and lungs (Study ID ● 273).

Lipid metabolism

Lovati et al. (1996) evaluated the effects of 15 days of continuous SO_2 exposure at 5 and 10 ppm on the lipid and carbohydrate metabolism of rats with and without hypercholesterolemia and diabetes. They observed a dose-dependent increase in plasma triglycerides at 10 ppm SO_2 and a reduction of HDL cholesterol levels. Conversely, the same concentration resulted in a decrease of plasma and liver triglyceride levels and an increase in plasma HDL cholesterol in diabetic rats. The results of this study suggest that SO_2 exposure can modify major lipid and glycemic indices (Study ID ▲ 152).

In guinea pigs exposed to 10 ppm SO_2 for 1 hour per day for 30 days, Haider (1985) investigated the effects of SO_2 on lipid metabolism in guinea pig organs. They observed variations in the concentrations of phospholipids, total lipids, cholesterol, gangliosides and C/P ratio in the liver, heart, lungs and kidney. Also observed were an increased in the rate of malonaldialdehyde formation and lipid peroxidation (Study ID ◆ 163).

Summary

Clinical and Epidemiology

No human clinical or epidemiology studies were identified that investigated this health outcome and fit the criteria.

Non-clinical

Continuous exposure of mice to 40 ppm for 4 to 11 days was reported to depress metabolism as measured by oxygen consumption. Decreased enzyme activity was observed in mice (20 ppm for 6 hours/day for 7 days) and rats (5 to 10 ppm for 5 hours/day for 7 to 28 days). Clinical significance of these observations was not discussed and is unclear.

Changes in lipid metabolism were reported in rats (continuous exposure to 5 and 10 ppm for 15 days) and guinea pigs (20 ppm for 1 hour/day for 30 days).

N. Nervous System

No clinical or epidemiology studies that fit the criteria were identified in this category.

Non-clinical

Behavioural

Petruzzi et al. (1996) observed acute and subacute behavioural changes in male and female mice exposed to 5, 12, and 30 ppm of near continuous exposure to SO_2 for 24 days. Changed behaviours included rearing, social interactions, grooming, digging and chamber-crossing (Study ID ▲ 214).

Fiore et al. (1998) exposed CD-1 mice to 5, 12, and 30 ppm SO_2 prenatally (first 14 days of pregnancy) and investigated changes in aggressive behaviour at adulthood. Changed behaviours included reduced tail rattling, freezing, social investigation and defensive postures. A 20-minute aggressive encounter was set up by pairing an exposed subject with an unexposed CD-1 male opponent of the same age, body weight, and isolation condition as the exposed subjects. Offensive and attack behaviours were unchanged (Study ID ◆ 217).

Biochemical

Haider et al. (1981) investigated the effects of SO_2 exposure at 10 ppm, 1 hour per day for 21 days on guinea pig brain lipids, lipid peroxidation and lipase activity. They found a significant depletion of total lipids and free fatty acids in all brain regions. Phospholipid, cholesterol, esterified fatty acid concentrations and the rates of lipid peroxidation and lipase activity were affected differently in different parts of the brain (Study ID ▲ 159). Haider et al. (1982) investigated the effects of SO_2 exposure at 10 ppm, 1 hour per day for 30 days on lipid levels, lipid peroxidation and lipase activity in rat brains. Lipid content and enzyme activity varied depending on brain area (Study ID ◆ 249).

Functional

Several studies investigated the effect of SO_2 exposure on respiratory reflex mechanisms. Rabbits were the species most frequently represented. However, other species examined included cats, ferrets, dogs and rats. These concur that bronchoconstrictive response is reflexive in nature. However, the mechanism of the reflex has not been conclusively determined (Barthelemy et al., 1988 – Study ID ▲ 197; Korpas and Widdicombe, 1983 – Study ID ◆ 153; Matsumoto et al., 1997 – Study ID ◆ 200; Wang et al., 1996 – Study ID ◆ 211; Davies et al., 1978b – Study ID ◆ 239; Davenport et al., 1984 – Study ID ◆ 244; Nadel et al., 1965 – Study ID ● 069; Mortola et al., 1985 – Study ID ● 141; Hanacek et al., 1991 – Study ID ● 161; Cho et al., 1968 – Study ID ● 167;

Citterio et al., 1985b – Study ID ▲ 194;
Citterio et al., 1985a – Study ID ● 195;
Davies et al., 1978a – Study ID ● 234;
Balchum et al., 1960 – Study ID ● 237).

Summary

Clinical and epidemiology
No human clinical or epidemiology studies were identified as fitting the criteria.

Non-clinical
Behavioural changes in rearing, social interactions, grooming, digging and chamber-crossing were reported in male and female mice exposed to 5, 12, and 30 ppm of near continuous exposure for 24 days. Male mice exposed to 5, 12, and 30 ppm prenatally exhibited changed aggressive behaviour in adulthood when subjected to an aggressive encounter with an unexposed mouse of the same age, body weight and isolation condition.
Changes in the lipid content of guinea pig and rat brains were reported for exposure to 10 ppm for 1 hour/day for 21 days and 30 days, respectively.
Several studies investigated the effect of SO_2 exposure on respiratory reflex mechanisms. These studies concur that the bronchoconstrictive response is reflexive, but the mechanism of the reflex has not been conclusively identified.

O. Olfactory System

Unlike for H_2S, there are no studies investigating the affect of SO_2 exposure on the sense of smell. Studies concerned with the effects of SO_2 on the nasal passages are described in the section on the respiratory system.

P. Reproductive System

Clinical studies
No clinical studies investigating this health outcome were located.

Non-clinical studies
Petruzzi et al. (1996) exposed adult male and female mice to 0, 5, 12, and 30 ppm SO_2 from 9 days before pregnancy to gestational day 12-14. There were no observed changes in reproductive performance or neurobehavioural development of the offspring (Study ID ▲ 214).
Singh (1982) investigated the teratogenicity of SO_2 exposure in mice. Pregnant mice were exposed to SO_2 concentrations of 0, 32, 65, 125, and 250 ppm from gestation days 7 through 17. On gestation day 18, the animals were sacrificed and the fetuses examined for teratological effects. No significant effect on the number of dead or reabsorbed fetuses and no significant teratological changes were observed. Several of the fetuses had hematomas at all levels of exposure and a significant decrease in the weight of pups exposed to 65 and 125 ppm was observed (Study ID ◆ 203)

Murray et al. (1979) investigated the embryotoxicity and teratogenicity of SO_2 in mice and rabbits exposed to 25 and 70 ppm, respectively. The mice were exposed on gestational days 6 through 15 and the rabbits were exposed on gestational days 6 through 18. SO_2 exposure had no effect on the dams of

either species. The number of fetuses per litter and the number of reabsorptions were not affected by exposure to SO_2 in either species. However, mean fetal body weight was decreased in mice litters. (Study ID ◆ 140). Fiore et al. (1998) tested whether SO_2 exposure produces social or agonistic behavioural changes in adult male mice exposed to SO_2 prenatally. The mice were exposed to 0, 5, 12, or 30 ppm SO_2 on gestational days 1 through 14. At adulthood the exposed mice underwent an aggressive encounter with a non-exposed male of the same age and body weight. There was a significant enhancement in body sniffing behaviour and self-grooming duration in the exposed mice. Other non-social behaviours were increased, whereas behaviours such as tail rattling, freezing and defensive behaviours decreased. Offensive and attack behaviours were not modified (Study ID ◆ 217).

Epidemiology studies

Dolk et al. (2000) investigated whether populations living within a 7.5 km radius of cokeworks in Great Britain had a higher risk of adverse perinatal and infant outcomes. SO_2 is a major pollutant from cokeworks. Highest exposure was assumed to be at distances 2 km from the cokeworks. Outcomes were obtained from recorded birth and death data. No evidence of increased risk of low birth weight, infant mortality, neonatal mortality, postneonatal mortality, respiratory postneonatal mortality or postneonatal Sudden Infant Death Syndrome and proximity to cokeworks. However, this study had several shortcomings that limit the reliability and utility of these results, one being the lack of accurate SO_2 exposure data (Study ID ● 003).

Summary

Clinical

No human clinical studies investigating this health outcome were found.

Non-clinical

No significant teratological or embryotoxicological effects were reported in studies on mice exposed to up to 250 ppm during gestation. No changes in reproductive performance or neurobehavioral development were reported in male and female mice exposed to up to 30 ppm during gestation. Some social or agonistic behavioural changes were reported during an aggressive encounter in adult male mice that had been exposed to up to 30 ppm during gestation.

Epidemiology

No moderate or high quality studies were identified for this health outcome.

Skin

Only one study mentioned effects of SO_2 exposure on skin (Study ID ▲ 159). This study was included in the **Signs and Symptoms** section of this report.

VI. Conclusions

The majority of the evidence from the scientific literature reviewed here refers to effects on the respiratory system. There is limited evidence of effects to other body systems, primarily from animal studies.

Evidence from Human Studies

The majority of the human studies investigated and reported respiratory effects. Both healthy subjects and those with respiratory illness (asthma or

chronic obstructive pulmonary disease) were included in the studies.
The most common effects reported in healthy subjects were increased airway resistance and bronchoconstriction, decreased maximum expiratory flow, and decreased pulmonary function. Some subjects reported dryness and irritation of the throat, general respiratory discomfort, and unpleasant taste and odours. Effects reported in asthmatic subjects were similar, but also included increases in asthma symptoms, wheezing, chest tightness, and dyspnea. The evidence suggests that subjects with respiratory illness are more susceptible to respiratory health effects from SO_2 exposure.
Other factors contributing to SO_2-induced effects were examined in these studies. Exercise seems to exacerbate the response to SO_2 in both healthy and asthmatic subjects. Cold and/or dry air also exacerbates the asthmatic response. In addition, the method of exposure affects the response, with forced mouth breathing eliciting a greater response than nasal or oronasal breathing. Clinical studies covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

The weight of evidence for exposures up to 30 minutes suggests that healthy humans can experience exposures to SO_2 up to 10 ppm with only transitory effects on pulmonary function, even under challenging conditions involving hyperventilation, mouth-only exposure, and heavy exercise. Transitory effects may be observed at concentrations as low as 0.75 ppm.
For exposures up to 30 minutes, asthmatics appear to demonstrate pulmonary effects at lower thresholds (0.1 ppm), although even in this population subgroup the clinical effects are transient and may or may not require intermittent pharmacologic intervention.

The weight of evidence for single exposures up to 4 hours and repeated exposures between 3 days and 3 weeks suggests that transitory pulmonary effects might be expected for asthmatics at exposure concentrations between 0.5 and 1 ppm and for healthy humans between 0.75 and 25 ppm, with some evidence for a concentration-dependent response in healthy subjects.

No high quality epidemiology studies or case reports were identified.
Epidemiology studies were divided into two types based on calculation of exposure concentration. One set of studies calculated exposures as increases in ambient concentration above a baseline or average concentration. Another set of studies reported exposure as discrete concentrations, either as average concentrations or a concentration range.
A weight of evidence evaluation is difficult for the epidemiology studies as the majority of these studies were ranked low quality. For the moderate quality studies, there were an equal number of studies that found insignificant or no associations between ambient SO_2 concentration and health outcomes as there were that did report an association. These studies were subject to substantial limitations due to misclassification of both exposure and outcome. The majority of these studies are ecological in nature with outcomes determined on an individual level and exposure determined at a population level. The

exposure data collected was generally for ambient levels. Since humans spend a large portion of their time indoors and travel through various microclimates during various activities, ambient levels will likely not be a good measure of exposure at the individual level. Subsequently, the major weakness observed in these epidemiology studies is the potential for exposure misclassification as a result of the exposure assessment methods. Much of the exposure and outcome data used in these studies is retrospective and from public records, which increases the probability of misclassification due to inconsistent diagnosis of disease status and bias. Many confounding factors cannot be accounted for when using these types of data.

In addition, SO_2 is just one element in a mixture of pollutants found in "air pollution". It is difficult to isolate the effects of SO_2 from those of other single pollutants or combinations of pollutants. Because of these substantial limitations, the confidence in the results and conclusions from these epidemiology studies could not be judged to be higher than moderate and in most cases the confidence was judged to be low. Associations, when reported, were generally weak. Associations were reported for decreased pulmonary function, and hospital admissions for asthma and other respiratory diseases. Reported symptoms included throat irritation, chest discomfort, restricted activity, shortness of breath, cough, dyspnea, and lower baseline function. Weak associations were reported in epidemiology studies for various mortality causes. However, the body of epidemiological evidence for mortality contains much variability and few studies in which we can have confidence, mainly due to the limitations discussed above.

There is little reliable evidence in the peer-reviewed scientific literature meeting the terms of reference for this report of human health effects involving the eye, kidney and liver, or the cardiovascular, gastrointestinal, metabolic, immunological, reproductive, or nervous systems.

Evidence from animal studies

Much of the animal evidence for respiratory effects concentrates on the mechanisms of action of health effects from SO_2 exposure. The clinical significance of much of the animal evidence is unclear and was not discussed in the studies themselves. Studies on respiratory effects were well represented. Reported respiratory effects included increased bronchoconstriction and specific airway resistance and decreased ciliary activity. Non-clinical studies covered a broad range of exposure durations. Therefore, the summaries of the findings are broken down by exposure time to facilitate comparison.

The concentrations in respiratory studies of animals exposed for **up to 2 hours** ranged between 0.5 ppm and 1000 ppm. For concentrations up to 100 ppm, effects reported were predominantly very mild respiratory effects and changes at the cellular or ciliary level. Above 100 ppm, pulmonary effects were more in evidence, with indications of changes to the lung. There is evidence of increasing severity of effect with increasing concentration.

In studies with exposures **between 2 and 24 hours**, mild respiratory effects and

delayed airway reactivity were reported with concentrations up to 40 ppm. Damage to the lungs was reported at concentrations of 800 ppm and 1225 ppm.

At exposures **between 1 and 7 days**, slight changes were observed in lung function and in response to virus challenges at concentrations between 0.1 ppm and 34.5 ppm. At the higher concentrations of 100 ppm and 600 ppm, changes to lung structure were reported.

Few respiratory studies investigated exposures **between 7 and 30 days**. One study reported changes in response to virus challenges with exposures up to 0.1 ppm. Other studies reported changes in lung biochemistry and some decrease in pulmonary function at concentrations between 10 and 600 ppm.

Only a few animal studies looked at the effect of SO_2 exposure on the liver or kidneys. However, there is some evidence of decreased levels of liver lipids and triglycerides and decreased enzyme activity in liver and kidney following SO_2 exposure.

There is some evidence that exposure to SO_2 can affect the metabolic system, in particular lipid metabolism, at exposure times of several days. This effect seems to differ depending on which organ of the body is investigated.
There is some evidence from animal studies that SO_2 exposure both as an adult and prenatally can affect behaviour in adult mice subjected to challenging conditions. There is also some evidence that exposure to SO_2 can affect the lipid content of the brain. The outcomes of both these studies are of unknown clinical significance and the number of studies is limited, although the quality of the studies suggests the results are reliable. It has been established in several species that bronchial restriction upon SO_2 exposure is a reflex reaction; however, the mechanism of this reflex has not been conclusively determined.

There is limited animal evidence for signs and symptoms, or effects on the eye, and reproductive, gastrointestinal, or cardiovascular systems found in the animal studies reviewed for this report.

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Key to Tables 1 through 9

Abbreviations for Tables

AC = children or adolescents with asthma or other chronic pulmonary disease
AA = adults with asthma or other chronic pulmonary disease
BAL = bronchoalveolar lavage
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
HA = healthy adults
HC = healthy children or adolescents
$MEF_{50\%VC}$ = maximum expiratory flow from one half vital capacity
MMEF = maximum mid-expiratory flow
MEFR = maximum expiratory flow rate
MNPCE = polychromatic erythrocyte micronuclei
PEF = peak expiratory flow
ROI = reactive oxygen intermediate
SRaw = specific airway resistance
V_{max50} = maximum flow calculated at 50% vital capacity
V_{max75} = maximum flow calculated at 75% vital capacity

Confidence Index Ranking

High ▲
Moderate ◆
Low ●

Table 1A – Respiratory Effects Associated With Short-term Exposure to SO_2: Human Clinical Findings – 1 to 5 Minute Exposures

Concentration ppm *(mg/m³)*	Effects	Exposure Duration
0.1 *(0.26)*	◆Bronchoconstriction at lower concentrations in dry air than humidified air (AA)[057]	3 min
0.5 *(1.3)*	◆Increased SRaw (AA)[061], greater with oral than nasal exposure (AA)[074]; with cold dry air (AA)[123] ◆Dryness, irritation, or burning of the throat (to 5 ppm; HA)[039] ◆Chest tightness, wheezing, dyspnea (and 1 ppm; AA)[064] ◆Increased bronchoconstriction(AA)[326]	3min, 3x30 min/5/3 min 1 to 5 min 1, 3, 5 min 5 min
0.60 *(1.6)*	◆Decreased respiratory function (AA)[314]	5 min
0.75 *(2)*	◆Increase SRaw with hyperventilation[318]	5 min
<1 *(<2.6)*	Chest tightness, wheezing, dyspnea, cough (AA)[093]	1,3, or 5 min
1 *(2.6)*	◆Increased SRaw (AA)[062,064]	4 min/1,3,5 min
2 *(5.2)*	◆Changes in SRaw (AA)[062]	4 min
10 *(26)*	◆Bronchial obstruction, returned to control by 45-60 min. post-exposure (AA)[260]	3 min

Table 1B – Respiratory Effects Associated with Short-term Exposure to SO_2: Human Clinical Findings – 6 to 10 Minute Exposures

Concentration ppm *(mg/m³)*	Effects	Exposure Duration
0.2 *(0.5)*	◆Increased respiratory frequency (AA)[071]	10 min
0.25 *(0.6)*	◆Increased SRaw (AA)[118]	10 min
0.3 *(0.8)*	◆Increased bronchoconstriction, returned to normal levels 30 min. post-exposure (and 0.6 ppm; AA)[097]	10 min
0.5 *(1.3)*	▲Dose-dependent change in respiratory function (to 1 ppm; AA)[077] ◆Reduction in FEV_1, $V_{max\,50}$, V_{max75}, (AA)[055]	10 min 10 min
0.60 *(1.6)*	◆Decreased respiratory function (AA)[304]	10 min
0.75 *(2)*	◆Reduction in FEV_1, increased total respiratory resistance (AC)[103] ◆Increased SRaw[304]	10 min 10 min
1 *(2.6)*	◆Reduction in FEV_1, $V_{max\,50}$, V_{max75} (AC)[038,102] ◆Slight reduction in FEV_1, $V_{max\,50}$, V_{max75} or increased bronchoconstriction after exercise (HC)[042]	30'r,10'e/10' 30'r,10'e
2 *(5.3)*	◆Changes in SRaw (AA)[303]	10 min
2.5 *(6.6)*	◆Decreased specific airway conductance greater with oral than nasal exposure (HA)[105]	10 min to 1 hr
5 *(13)*	◆SRaw exhibited in all subjects[375]	10 min
15 *(39)*	◆Increased pulmonary flow resistance; greater from oral than nasal exposure (HA)[054]	10 min

Table 1C – Respiratory Effects Associated with Short-term Exposure to SO_2: Human Clinical Findings – 11 to 30 Minute Exposures

Concentration ppm *(mg/m³)*	Effects	Exposure Duration
0.1 (0.3)	◆Slight reduction in FEV_1, $V_{max\,50}$ (AC)[ ]	15 min
0.5 *(1.3)*	▲Increased SRaw (AA)[109] ◆Dose-dependent effect on FEV_1, $V_{max\,50}$, V_{max75} (to 1 ppm; AA)[ ] ◆Increased SRaw -greater with oral than nasal exposure (AA)[ ]	30 min 30 min 3x30 min
1 *(2.6)*	◆Reduction in FEV_1, $V_{max\,50}$, V_{max75} (AC)[038], (AA)[ ] ◆Slight reduction in FEV_1, $V_{max\,50}$, V_{max75} or increased bronchoconstriction after exercise (HC)[042] ◆Decreased $MEF_{50\%VC}$ (HA)[070] ◆Functional impairment of alveolar macrophages (to 5.0 ppm)[ ]	30'f,10'e,20 min 30'f,10'e 15 min 30 min
2 *(5.3)*	◆Difference in ventilatory parameters between forced oral and free-breathing exposures (HA)[266]	30 min
2.5 *(6.6)*	◆Decreased specific airway conductance greater with oral than nasal exposure (HA)[ ] ◆Dose-dependent increase in ciliary beat frequency (to 12.5 ppm)[ ]	10 min to 1 hr 30 min
4 *(10)*	◆Increased alveolar activity in BAL (and 8 ppm; HA)[083]	20 min
8 *(21)*	◆Increases in macrophages, lymphocytes, and mast cells in BAL (HA)[ ]	20 min

Table 1D – Respiratory Effects Associated with Short-term Exposure to SO_2: Human Clinical Findings – 31 Minute to 4 Hour Exposures

Concentration ppm *(mg/m³)*	Effects	Exposure Duration
0.5 *(1.3)*	▲Increased SRaw (AA)[081] ◆Reduction in FEV_1, $V_{max\,50}$, V_{max75} (AC)[099]	75 min 50 min
0.75 *(2)*	▲Increased SRaw (HA)[060] ◆Increased SRaw initially, decreased to pre-exposure levels after 1 hr of exposure (AA)[079]	2 hours 3 hours
1 *(2.6)*	▲Decreased spirometric function (HA)[096] ◆Increased SRaw (HA)[047], (AA)[078]	4 hr d,3d/wkx3 2hr 1hr
2.5 *(6.6)*	◆Decreased specific airway conductance greater with oral than nasal exposure (HA)[ ]	10 min to 1 hr
5 *(13)*	◆Decreased MMFR, increased bronchial clearance (HA)[045,053] ◆Decreased nasal mucous flow rate (HA)[048]	2.5 hr 3 hr 4 hr

Table 1E – Respiratory Effects Associated with Short-term Exposure to SO_2: Human Clinical Findings – >4 Hour Exposures

Concentration ppm *(mg/m³)*	Effects	Exposure Duration
1 *(2.6)*	▲Decreased spirometric function (HA)[096] ◆Decreased nasal mucous flow rate (HA)[063] ◆Discomfort proportional to SO_2 concentration (to 25 ppm; HA)[ ]	4 hr d,3d/wkx3 6 hr/d x 3d 6 hr/d x 3d

Table 2 – No Effects Associated With Short-term Exposure to SO_2: Human Clinical Findings

Concentration ppm *(mg/m³)*	Observations	Exposure Duration
0.20 *(0.52)*	◆ No significant effect on pulmonary function in asthmatics (AA)[067]	6 hours
0.40 *(1.0)*	◆ No change in FEV_1 in healthy males with moderate exercise (HA)[051,049]	2 hours
0.50 *(1.3)*	▲ No significant effect in pulmonary function parameters for asthmatics (mouthpiece breathing; moderate exercise; from 0.25 ppm; AA)[075] ▲ No effect on pulmonary function parameters (HA)[073]	1 hour (alternating rest with 10 min exercise) 3 hours
0.60 *(1.6)*	◆ No significant pulmonary effects for normal and atopic subjects with exercise (from 0.2 ppm; HA,AA)[309]	1 hour (incl. 3 – 10 min exercise periods)
0.75 *(2.0)*	▲ No effect on pulmonary function during or after exposure with exercise in healthy subjects (HA)[043]	4 hours (with 2 – 15 min exercise periods)
0.80 *(2.1)*	◆ No effect on pulmonary function for patients with COPD with exercise (from 0.4 ppm; AA)[101]	1 hour
1 *(2.6)*	◆ No changes in pulmonary function for healthy subjects (from 0.25 ppm; HA)[306] ◆ No pulmonary function effects with exercise (HA)[122] ◆ No changes in pulmonary function or bronchial reactivity (HA)[040]	40 min (exercise) 2 hours (3 – 30 min exercise periods) 4 hr/d, 3d/wk for 3 wk
2 *(5.2)*	◆ No changes in pulmonary function with free breathing, forced oral, and forced nasal (HA)[266] ◆No change in pulmonary function with exercise (HA)[047]	30 min 2 hours
3.6 *(9.4)*	◆ No significant changes in pulmonary function parameters after exposure with normal breathing and hyperventilation (from 1.1 ppm; HA)[113]	30 min

Table 3A – "Positive" Respiratory Effects Associated With Short-term Exposure to SO_2: Animal Toxicology Studies – Up to 2 Hour Exposures

Concentration ppm (*mg/m³*)	Effects	Exposure Duration
0.5 (*1.3*)	▲*Dose-dependent increases in lung resistance (and 5 ppm; Rabbits)*	*45 min*
1 (*2.6*)	◆*Increased respiratory resistance; decreased compliance (Guinea pigs)* ◆*Dose-dependent increase in bronchoconstriction (to 2.5 ppm; Guinea pigs)* ◆*Decreased proportion of macrophages in white cells (to 5 ppm; Guinea pigs)*	*1 hr* *10 min-1 hr* *10 min*
10 (*26*)	◆*Inhibition of ciliary movement (Rabbits)*[468]	*1 hr*
15 (*39*)	◆*Dose-dependent increased in ciliary activity (to 77 ppm; guinea pigs)*	*2 to 6 min*
17 (*44*)	◆*Dose-dependent respiratory depression (to 298ppm; Mice)*	*10 min*
50 (*131*)	▲*Reduction in pulmonary macrophage endocytosis(Hamsters)*[574] ◆*Reduced dynamic compliance (Dogs)*[189]	*Unreported* *15 min*
100 (*262*)	▲*Increase in minute volume (Chickens)*[183]	*60 min*
200 (*524*)	◆*Decreased breathing frequency, increased tidal volume (Rabbits)*[244]	*15 – 20 min*
500 (*1310*)	▲*Decreased SRaw(Chickens)*[183] ◆*Changes to bioelectric properties and increased nonelectrolyte permeability (Dogs)*[157]	*60 min* *75 min*
800 (*2096*)	◆*Reduction in minimal and maximal pulmonary surface tension (Rats)*[155]	*1 hr*
1000 (*2620*)	▲*Initial decrease then increase in SRaw, increased respiratory frequency, decreased minute volume (Chickens)*[183]	*60 min*

Table 3B – "Positive" Respiratory Effects Associated With Short-term Exposure to SO_2: Animal Toxicology Studies – 2 Hour to 1 Day Exposures

Concentration ppm (*mg/m³*)	Effects	Exposure Duration
4 (*10*)	◆*Increased airway reactivity in asthmatic sheep 24 hr after exposure (Sheep)*	*4 hr*
10 (*26*)	◆*Increased airway reactivity in asthmatic sheep 24 hr after exposure (Sheep)* ◆*Lesions of olfactory and respiratory epithelium (Mice)*[19] ◆*Decrease in thickness of olfactory mucosa, severe rhinitis (Mice)*[18]	*4 hr* *4 to 72 hr* *4 to 72 hr*
20 (52)	◆*Delayed early clearance of upper respiratory tract (Rats)*[256]	*4 hr*
40 (*105*)	◆*Dose-dependent decrease in % SO_2 retention, respiratory rate, minute volume, increase in tidal volume (Rats)*[253]	*2 hr*
800 (*2096*)	◆*Gradient of decreasing damage in the tracheobronchial tree(Rats)*	*8 hr*
1225 (*3210*)	◆*Pulmonary edema, greater reduction in surface tension (Rats)*	*2 hr*

Table 3C – "Positive" Respiratory Effects Associated With Short-term Exposure to SO_2: Animal Toxicology Studies – 1 Day to 7 Day Exposures

Concentration ppm (*mg/m³*)	Effects	Exposure Duration
0.1 *(0.26)*	▲*Increased respiratory pause (Guinea pigs)*[259] ◆*Slight reduction in lung clearance (Rats)*[235] ◆*Increased antigen-specific antibodies in serum and bronchoalveolar fluid (Guinea pigs)*[133]	*5 hr/d, 5d* *70 hr* *8 hr/d, 5 d*
3.4 *(8.9)*	◆*Increased incidence of pneumonia after exposure to SO_2 (to 34.5 ppm; Mice)*[182]	*7 d*
6 *(16)*	◆Inhibition of virus growth (Mice)[238]	*7 d*
10 *(26)*	◆*Lesions of olfactory and respiratory epithelium (Mice)*[191] ◆*Decrease in thickness of olfactory mucosa, severe rhinitis (Mice)*[191]	*4 to 72 hr* *4 to 72 hr*
100 *(262)*	◆*Decreased glutathione concentration and inflammation (Rats)*[251]	*5hr/d, 7 to 28d*
600 *(1572)*	◆*Increased mucosal permeability (Rats)*[206]	*30 to 100 hr*

Table 3D – "Positive" Respiratory Effects Associated With Short-term Exposure to SO_2: Animal Toxicology Studies – Greater Than 7 Day Exposures

Concentration ppm (*mg/m³*)	Effects	Exposure Duration
0.03 *(0.08)*	◆*More rapid and more severe inflammatory response to influenza infection (to 0.1 ppm; Mice)*[207]	*4 weeks*
10 *(26)*	◆*Increased concentrations of cholesterol, total lipids, gangliosides and decreased phospholipids (Guinea pigs)*[163]	*1 hr/d x 30d*
100 *(262)*	◆*Decreased glutathione concentration and inflammation (Rats)*[251]	*5hr/d, 7 to 28d*
150 *(393)*	◆*Increased lung resistance, decreased breathing frequency (Rabbits)*[239]	*12 x 3hr*
600 *(1573)*	◆*Increase in solid material recovered by bronchial lavage (Rats)*[250]	*3 hr/d for 9,18, or 30 d*

Table 4A Epidemiology: Mortality Endpoints Associated with Increases in Short-term Exposure to SO_2: Statistically Significant / Positive Findings

Exposure Increase ppb (µg/m³)	Effect	Baseline Exposure ppb (µg/m³)	Study duration	Study Population	Reported Association
4.0 ***(10)***	● Increase in daily death count for people >65 years old (lag 3d)[414]	1.9 – 22.9 *(5-60)*	2 years	N/A	2.4% increase in daily death count
4.0 ***(10)***	● Weak increases in daily deaths associated with an increase in SO_2 concentration[407]	4.2 – 16.8 *(11-44)*	~ 6 years	N/A	RR: 1.0027 (95% CI: 1.0018 – 1.0037)
4.0 ***(10)***	● Slight association with respiratory mortality when SO_2 increased[422]	Mean: 6.4 ± 4.4 *(17±12)*	3 years	17 ± 5 respiratory deaths/day	RR: 1.015 (95% CI: 1.001 – 1.029)
5.7 ***(15)***	● Significant increase in stroke mortality with a 2d lag[415]	Mean: 12.1 ± 7.4 3.0 – 46.0 *(32±19)* *(7.9-121)*	3 years	15.3 stroke deaths/day	2.8% increase (95% CI: 0.8% – 5.0%)
Rouen: **7 – 14** ***(18-37)*** **Le Havre:** **4 – 13** ***(10-34)***	◆ Significant increases in respiratory mortality associated with increases in SO_2 concentrations[430]	Rouen: Summer: 9.1 *(24)* Winter: 13.5 *(35)* Le Havre: Summer:10.6 *(28)* Winter:15.1 *(40)*	5 years	Rouen: 21 883 deaths Le Havre: 13 885 deaths	Rouen: 8.2% increase (95% CI: 0.4% – 16.6%) Le Havre: 3% increase (95% CI: 0.8% – 5%)
7.8 ***(20)***	● RR for total mortality >1 for neonates and people >65 yrs. RR for respiratory mortality >1 for people aged 2 -64[408]	Mean: 11.1 ± 7.0 2.4 – 46.0 *(29±18)* *(6-121)*	4 years	Total deaths: Postneonates: 1045 2-64 yrs: 67 597 >65: 100 316	N/A
17.43 ***(46)***	● Significant association between increased SO_2 and increases in ischemic stroke mortality[397]	21.8 ± 18.8 *(57±49)*	6 years	7.4 deaths/day from stroke	RR: 1.04 (95% CI: 1.01 – 1.08)
19 ***(50)***	● Significant association with increased total mortality, CV mortality, and respiratory mortality[407]	N/A	5 years	9 cities 260 000 – 9 million people/city	Total deaths RR 1.036 (95% CI: 1.021 – 1.052)
19 ***(50)***	◆ Significant increases observed for respiratory and CV deaths[352]	Mean: 46.76 2.12 – 314.57 *(123)* *(5.6-824)* Max: 100.22 4.71 – 635.69 *(263)* *(12±1666)*	5 years	6.43 deaths/day	Total mortality RR: 1.06 (95% CI: 1.02 – 1.09) Respiratory mortality :1.05 (95% CI: 1.02 – 1.09) CV Mortality RR: 1.08 (95% CI: 1.03 – 1.12)
19 ***(50)***	◆ Significant increase in daily mortality in Western European cities[336]	Median: 5.0 – 28.2 *(13-74)* Mean winter: 11.4 – 125.9 *(30-330)*	5 – 14 years	12 cities	3% increase (95% CI: 2% – 4%)

Table 4A Epidemiology: Mortality Endpoints Associated with Increases in Short-term Exposure to SO_2: Statistically Significant / Positive Findings *(continued)*

Exposure Increase ppb (µg/m³)	Effect	Baseline Exposure ppb (µg/m³)	Study duration	Study Population	Reported Association
38 *(100)*	◆ Association with total mortality, elder mortality (>70 yrs) and CV mortality for whole year and winter. Association with total mortality, elder mortality, CV and respiratory mortality in summer[345]	Mean 24-hour Winter: 17.6 0.8 – 61.1 *(46)* *(2-160)* Summer: 13.9 2.1 – 44.5 *(36)* *(5.5-117)*	6 years	Median total mortality: Winter: 48/d Summer: 43/d	All cause RR: 1.13 Elderly RR: 1.13 CV RR: 1.14
38 *(100)*	◆ SO_2 increases associated with an increased risk of daily mortality[349]	Average: 19.6±11.4 *(51±30)* Range: 2.3 – 137.8 *(6-361)*	1826 days	Mean daily deaths: 37.2±8.0	RR: 1.12 (95% CI: 1.07 – 1.16)
38 *(100)*	● Regression analysis estimates a significant association between increased SO_2 and increased mortality[359]	>76.3 ppb 19% of time *(>200)* Max: 229 *(600)*	1167 winter days	17.3 deaths/d	RR:1.19
38 *(100)*	● SO_2 increases associated with excess mortality[391]	Means: 40.8 – 83.6 *(107-219)*	8 years (winters)	1987 pop: 1 284 553	N/A
38 *(100)*	● Associated with respiratory mortality (2d lag) and CV mortality (2 and 3d lag)[461]	Mean: 81.2 12.2 – 217.9 *(21)* *(32-571)*	365d	Mean daily deaths: Resp:9.6 CV:2.9	Resp RR (2d lag): 1.11 (95% CI: 1.02 0 1.22) CV RR (2d lag): 1.10 (95% CI: 1.02 – 1.20) (3d lag): 1.20 (95% CI: 1.11 – 1.30)
38 *(100)*	● Significant increase in total mortality when using single pollutant model[483]	21 *(55)*	7 years	Population: 1 688 710	5% increase (95% CI: 3% - 7%)
38 *(100)*	● Some significant associations depending on the combination of age, gender, and season used[465]	Annual mean: Station 1: 26.9±19.9 1.5 – 182.8 *(70±52)* *(3.9-479)* Station 2: 30.1±17.1 3.4 – 142.7 *(79±45)* *(8.9-374)*	6 years	Annual: Total deaths/d: 60.3±11.3 CV deaths/d: 23.7±6.5 Resp deaths/d: 5.8±3.1	N/A
100 *(262)*	● Association with mortality in spring and winter[334]	Daily means: Spring: 16.8 *(44)* Summer: 15.7 *(41)* Fall: 17.8 *(47)* Winter: 25.4 *(67)*	15 years	Daily deaths: S: 54.4(75) S:51.0(78.3) F:52.6(66.5) W:59.3(97.4)	Spring RR: 1.19(95% CI: 1.06 – 1.33) Winter RR: 1.21 (95% CI: 1.09 – 1.35)

Table 4A Epidemiology: Mortality Endpoints Associated with Increases in Short-term Exposure to SO_2: Statistically Significant / Positive Findings *(continued)*

Exposure Increase ppb (µg/m³)	Effect	Baseline Exposure (ppb)	Study duration	Study Population	Reported Association
355 *(930)*	● Increase in mortality observed with increase in SO_2[337]	Median daily Mean:75.2 3.8-1161 *(197) (10-3566)* Max:160 3.8-1892.7 *(419) (10-4980)*	10 years	Population: 107,000 Median deaths/d 6	RR: 1.10 (p=0.011)
1 standard deviation (?)	● Increased SO_2 associated with increase in total deaths[434]	Mean: 2.8±1.7 0.3 – 15.4 *(7.3 ±4.5) (0.79-40)*	2 years	30-40 deaths/day	RR: 1.0027 (95% C.I: 1.0018 – 1.0073)
"Doubling" concentration	◆ Risk of all cause mortality increase associated with increases in SO_2 concentration[338]	Mean: 39 *(102)* Max: 240 *(629)*	334 d	Population: 1 419 123	All cause increased risk: 11% (95% CI: 5% -16%)

Table 4B Epidemiology: Mortality Endpoints Associated with Increases in Short-term Exposure to SO_2: Insignificant / No Associations Found

Exposure Increase ppb (µg/m³)	Effect	Baseline Exposure (ppb)	Study duration	Study Population	Reported Association
4 *(10)*	● No significant association with total or CV mortality[480]	Mean: 22.6 7.2 – 52.8 *(59) (19-138)*	1 year	2.2 million	Total mortality RR: 1.007 (95% CI: 0.56 – 1.062) CV mortality RR: 1.028 (95% CI: 0.937 – 1.129)
4 *(10)*	● No association with daily mortality[355]	Mean: 15.2±5.9 2.7 – 40.3 *(40±15) (6.3-106)*	2 years	Mean total daily mortality: 17.49±5.03	Total mortality RR: 1.007 (95% CI: 0.999 – 1.015) Total mortality (>70yrs) RR: 1.009 (95% CI: 1.00 – 1.21) CV mortality RR: 1.012 (95% CI: 0.995 – 1.026)
4 *(10)*	● For single city analysis of all 13 cities in study, there were no associations between SO_2 and mortality[400]	Daily mean range: 3.1 – 17.0 *(8.1-45)*	6 years	Mean total daily deaths: 2.5 – 60.9 Population ranges: 134 000 – 2.9 million	N/A

Table 4B Epidemiology: Mortality Endpoints Associated with Increases in Short-term Exposure to SO_2: Insignificant / No Associations Found *(continued)*

Exposure Increase ppb (µg/m^3)	Effect	Baseline Exposure (ppb)	Study duration	Study Population	Reported Association
7.8 *(20)*	● Total mortality RR<1 for 2-64 year olds; respiratory mortality RR<1 for postneonates and people ≥65 yrs[408]	Mean: 11.0±7.0 2.4 – 46.0 *(29±18)* *(6-121)*	4 years	Total deaths Postneonates: 1045 2-64 yrs: 67 597 ≥65: 100 316	N/A
12.9 *(34)*	● No significant associations with total mortality[389]	Mean: 6.6±4.4 0.1 – 39.8 *(17±12)* *(0.26-104)*	14 years	N/A	RR: 1.08 (95% CI: 0.37 – 1.78)
7 – 17 *(18-45)*	● No significant association between ambient SO_2 concentration increases and all-cause mortality in London[365]	24h average: 12.2±4.5 *(32±12)*	5 years	All cause deaths/d: 175.5±27.0	RR: 1.01 (95% CI: 1.00 – 1.03)
17.43 *(46)*	● Insignificant association with hemorrhagic stroke mortality[397]	21.8±18.8 *(57±49)*	6 years	Stroke deaths/d: 7.4	N/A
19 *(50)*	◆ Insignificant association with mortality for Central Eastern European cities[336]	Mean: 46.76 2.12 – 314.57 *(123)* *(5.6-824)* Max: 100.22 4.71 – 635.69 *(263)* *(12-1666)*	5 -14 years	12 cities	0.8% (95% CI: -0.1% - 2.4%)
38 *(100)*	● No association with total daily mortality when gender, age, and cause of death are not separated out from entire population of North Bohemia[479]	Mean: 38.1±34.2 3.2 – 376.5 *(100±90)* *(8.4-987)*	12 years	Total all cause deaths: Men: 45 074 Women: 41 206	N/A
38 *(100)*	◆ No association found for daily mortality, regardless of lag day[377]	Mean: 5.0 *(13)* Max: 53.0 *(139)*	6 years	713 000	Current day RR: 1.042(95% CI: 0.943 – 1.151) 1d lag RR: 1.048 (95% CI: 0.952 – 1.154) 2d lag RR: 1.016 (95% CI: 0.923 – 1.119)

Table 4B Epidemiology: Mortality Endpoints Associated with Increases in Short-term Exposure to SO_2: Insignificant / No Associations Found *(continued)*

Exposure Increase ppb (µg/m³)	Effect	Baseline Exposure (ppb)	Study duration	Study Population	Reported Association
38 *(100)*	● Insignificant association with total mortality (2 and 3d lag); insignificant association with respiratory mortality (3d lag)[461]	Mean: 81.2 12.2 – 217.9 *(31.8)* *(32-571)*	365d	Daily Total: 9.6 Resp: 2.1 CV: 2.9	Total mortality RR 2d lag: 1.04 (95% CI 1.00 1.09) 3d lag: 1.04 (95% CI 0.99 1.08) Respiratory mortality 3d lag: 1.00 (95% CI 0.91 1.10)
38 *(100)*	◆ Insignificant effect on respiratory mortality[345]	Mean 24-hour Winter: 17.6 0.8 – 61.1 *(46)* *(2-160)* Summer: 13.9 2.1 – 44.5 *(36)* *(5.5-117)*	6 years	Median total mortality: Winter: 48/d Summer: 43/d	N/A
38 *(100)*	◆ Insignificant association with increased 24hr SO_2 concentrations and daily count of deaths[351]	Mean: 11.3 *(30)* Median: 8.8 *(23)* 5th centile: 2.7 *(7)* 99th centile: 47.7 *(125)*	5 years	Daily average deaths: 37	N/A
38 *(100)*	● Insignificant associations depending on combination of gender, age, and season[465]	Annual mean: Station 1: 26.9±19.9 1.5 – 182.8 *(70±52)* *(3.9-479)* Station 2: 30.1±17.1 3.4 – 142.7 *(79±45)* *(8.9-118)*	6 years	Annual: Total deaths/d: 60.3±11.3 CV deaths/d: 23.7±6.5 Resp deaths/d: 5.8±3.1	N/A
100 *(262)*	● Insignificant association with mortality in the summer and fall[334]	Daily means: Spring: 16.8 *(44)* Summer: 15.7 *(41)* Fall: 17.8 *(47)* Winter: 25.4 *(67)*	15 years	Daily deaths: S: 54.4(75) S:51.0(78.3) F:52.6(66.5) W:59.3(97.4)	Fall: RR = 1.14; 95% CI 1.00-1.29 Summer not reported
380 *(1000)*	● No significant association between SO_2 and daily deaths[332]	Range of means: 69 – 159.9 *(181-419)*	14 winters	292 deaths/d	N/A
1 standard deviation (?)	● Insignificant association with respiratory deaths or CV deaths[434]	Mean: 2.8±1.7 0.3 – 15.4 *(7.3±4.5)* *(0.79-40)*	2 years	30-40 deaths/day	N/A

Table 4C Epidemiology: Mortality Endpoint Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations – Positive / Statistically Significant Findings

Exposure level ppb (µg/m³)	Effect	Study Duration	Study Population	Reported Statistical Association
Daily average: 5.4 ***(14)*** **0.7 – 10.5** ***(1.8-27.5)***	● Increased mortality risk associated with SO_2 exposure [395]	11 years	816 991 deaths Population: 10.8 million	1.4% increased risk ($p<0.01$)
6.5 ***(17)***	◆ Significant association with mortality during the cool season[464]	1096 days	N/A	Total mortality RR: 1.04 (95% CI: 1.02 – 1.07) Respiratory mortality RR: 1.04 (95% CI: 1.00 – 1.09) CV mortality RR: 1.07 (95% CI: 1.02 – 1.11)
8 – 47 ***(21-123)***	● Statistically significant increase in daily mortality for daily means in range[348]	4018 d	Median cases/day: 29	3% increase in daily mortality
17.25±10.73 ***(45±28)***	● SO_2 concentrations associated with excess deaths in po;ulation[366]	2192 d	243.2 deaths/day	20% excess deaths attributed to SO_2
Marseilles: 19.3 ***(51)*** **Lyons: 24.8** ***(65)***	● Significant association between SO_2 concentrations and respiratory mortality up to 10d after exposure[002]	N/A	2 cities	N/A
Zurich: 35.4±35.5 ***(93±93)*** **Basle: 26.5±25.3** ***(69±66)*** **Geneva: 40.2±32.7** ***(105±86)***	◆ Significant association with respiratory mortality in Zurich and Geneva; Significant association with CV mortality in Basle and Geneva; Significant association with total mortality and mortality in people >65 in Basle and Geneva[403]	5 years	Total mortality per day: 8.8 – 21.7	N/A
>40 ***(>105)***	● SO_2 concentration a significant predictor of respiratory mortality with 1d lag[412]	20 months	Population: 2.4 million Deaths/day: 22.1±4.9	N/A
>76.3 ***(>200)***	● Association between daily maximum SO_2 and daily mortality[359]	1167 winter days	Deaths/d: 17.3	Correlation coefficient: 0.141 ($p<0.001$)
>88.8 ***(>232)***	● Mean daily 1-hour maximum associated with daily respiratory mortality[351]	5 years	Deaths per day: 37	N/A
>190 ***(>498)***	● Excess mortality associated with SO_2 exposure[012]	4 years	New York and New Jersey metropolitan area	2% excess mortality observed

Table 4C Epidemiology: Mortality Endpoint Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations – Positive / Statistically Significant Findings *(continued)*

Exposure level ppb (µg/m³)	Effect	Study Duration	Study Population	Reported Statistical Association
1 – 316 *(2.6-828)*	◆ Significant positive association with SO_2 exposure and respiratory deaths[462]	10 years	~1.5 million	Same day RR: 1.12 (95% CI: 1.05 – 1.23) Previous day exposure RR 1.16 (95% CI: 1.05 – 1.29)
200 (low) *(524)* **400 (high)** *(1048)*	● Additional daily deaths associated with SO_2 exposure[463]	5 years	N/A	Additional 10 – 20 deaths expected

Table 4D Epidemiology: Mortality Endpoint Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations – Statistically Insignificant Findings / No Associations

Exposure level ppb (µg/m³)	Effect	Study Duration	Study Population	Reported Statistical Association
Mean: 6±4 *(16±10)*	● No association between SO_2 concentration and respiratory mortality in children in Sao Paolo, Brazil[442]	1 year	Respiratory deaths d: 3.04±2.11 Nonresp. Deaths d: 5.41±2.44	N/A
50th centile average: 6.81 5.0 – 9.1 *(18)* *(13-24)*	● When all confounders are controlled for, SO_2 concentration does not have any effect on mortality in the Netherlands[356]	8 years	N/A	N/A
6.9 *(18)*	◆ No significant association with any mortality measure during the warm season[464]	1096 d	N/A	Total mortality RR: 1.02 (95% CI: 0.99 – 1.04) Respiratory mortality RR: 1.02 (95% CI: 0.99 – 1.09) CV mortality RR: 1.01 (95% CI: 0.97 – 1.05)
<11.4 *(<30)*	● Less mortality observed than expected at the reported concentrations[012]	4 years	New York and New Jersey metropolitan areas	1.5% less mortality than expected
Mean: 15±6 *(39±16)*	● No association between changes in SO_2 concentration and mortality in Los Angeles County[443]	9 years	Total deaths day: 152	N/A

Table 4D Epidemiology: Mortality Endpoint Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations – Statistically Insignificant Findings / No Associations *(continued)*

Exposure level ppb (µg/m³)	Effect	Study Duration	Study Population	Reported Statistical Association
Means: **W:16.3±18.1** ***(43±47)*** **Sp:7.7±7.2** ***(20±19)*** **S:4.5±1.9** ***(12±5)*** **F:7.8±6.4** ***(20±17)***	● No significant association with SO_2 concentration and total mortality or cause specific mortality for any season[354]	4 years	Total deaths: 19 062	Total mortality RR: 0.998 (95% CI: 0.96 – 0.99)
Low quintile: ***<5 (<13)*** **High quintile:** ***>22 (>58)***	● Insignificant positive association between neonatal respiratory mortality when comparing low to high quintiles[440]	2 years	Live births: 222 000 Neonate deaths: 1819 Postneonate deaths: 880	RR: 3.91 (95% CI: 0.90 – 16.9); p=0.062
Mean: **21** ***(55)***	● No significant association between SO_2 and total mortality when TSP and SO_2 are considered simultaneously[483]	7 years	Population: 1 688 710 Deaths/day: Total: 22.1 Cancer: 10.5 CV: 0.89 Pneumonia: 1.44	N/A
Marseilles: **19.3** ***(51)*** **Lyons: 24.8** ***(65)***	● No association with CV deaths[002]	N/A	2 cities	N/A
11.07 – 28.3 ***(29-74)***	● Inconsistent associations between SO_2 and CV mortalities – associations were both positive and negative[350]	4 cities: 2863 – 4747 days	Deaths/day: 13 - 27	N/A
0 – 40 ***(0-105)***	● No association between SO_2 and ability to predict respiratory mortality[412]	20 months	Population: 2.4 million Deaths/d: 22.1±4.9	N/A
Zurich: **35.4±35.5** ***(93±93)*** **Basle:** **26.5±25.3** ***(69±66)*** **Geneva:** **40.2±32.7** ***(105±86)***	◆ No association with respiratory mortality in Basle; No association with total, >65 mortality, or CV mortality in Zurich; Association between SO_2 and mortality is negative at high concentrations in Basle[403]	5 years	Total mortality/d: 8.8±21.7	N/A
Hourly max: **60** ***(157)***	◆ No association between SO_2 concentration and mortality[458]	2496 days of observation	N/A	N/A
>76.3 ***(>200)***	● Insignificant association with mortality in males ≤65 yrs old[359]	1167 winter days	Deaths/d: 17.3	N/A

able 5A Epidemiology: Respiratory Health Effects Associated with Incremental Increases in Short-term Exposure to SO_2: Statistically Significant / Positive Findings

Exposure Increase ppb ($\mu g/m^3$)	*Effect*	*Baseline Exposure ppb* ($\mu g/m^3$)	Study Duration*	Study Population+	Reported Association
2.5 (8-hr average) *(6.6)*	● Increase in "bothersome" and "more severe" symptoms in asthmatics[413]	4.6 ± 3.0 *(12±7.9)*	3 months	N = 22	[illegible]
3.8 *(9.9)*	● Association with hospital admissions for heart disease and COPD[481]	6.5 Range: 1.0-26.1 *(17)* *(Range: 2.6-68)*	1 year	[illegible] Resp: 88,[illegible] CV: 54-177 d	[illegible] CI 1.012 ± 0.08) All ages OR 1.013 (95% CI 1.004-1.021)
4.0 (hourly) *(11)*	● Increased "bothersome" asthma symptoms in children ages 10-16[413]	7.0 ± 4.0 *(18 ± 10)*			[illegible] CI 1.03-1.55)
4.0 *(11)*	◆ "Small" association with increased hospital respiratory admissions[423]	6.8 ± 4.7 *(18 ± 12)*	2 years	Avg. admissions d: (Hong Kong/London) Asthma: 7.8,14.1 Resp.: 91.3,58.3 Cardiac: 98.7,121.1 IHD: 36.0,51.3	Not reported
4.4 *(12)*	● Elevated risk for hospital admissions for asthma in children < 15 yrs old[398]	7.7 ± 3.3 *(20 ± 8.6)*	2 years	6436 asthma admissions	OR 1.11 (95% CI 1.06-[illegible]
4.5 (6d moving avg.) *(12)*	● Increased chronic lower respiratory disease emergency visits in elderly[399]	7.1 ± 4.0 *(19 ± 10)*	2 years	13,163 emerg. Visits (2300 respiratory)	[illegible] (Range: 4.14%-31.85%)
5.3 *(14)*	● Log-linear relation with incidence of acute childhood wheezy episodes in asthmatics[364]	8.4 ± 5.3 *(22 ± 14)*	~ 1 year	Cases: 1025 Controls: 4285	OR 1.12 (95% CI 1.05-[illegible]
5.7 (warm) *(15)* **7.8 (cool)** *(20)* **6.9 (all-yr)** *(18)*	● Increase in number of physician consults for respiratory disease[410]	7.8 ±2.5 (warm) *(20 ± 6.6)* 8.4 ± 3.4 (cool) *(22 ± 8.9)*	~ 2 years	Avg. daily consults: Young: 73.9±50.2 Adult: 96.3±62.6 Elderly: 15.5±11.3	[illegible] Cool: 5.5% (2.4%-8.7%) All yr: 3.5% (1.4%-5.8%) [illegible] Warm: 4.6% (1.5%-[illegible]
6.8 *(18)*	● Increased daily GP consultations for lower respiratory disease in children (strongest association). Other tested associations were not statistically significant [469]	Mean daily (winter): 8.4 ± 3.4 *(22 ± 8.9)*	~ 2 years	Consults d: (Asthma/other LRD) Young: 14.0,39.7 Adult: 17.8,73.8 Elderly: 3.6,41.4	5.8% (95% CI 1.6%-[illegible]
7.6 *(20)*	● Increased emergency room visits for asthma[456]	14.5 ± 8.32 Range: 1.1-53.8 *(38 ± 22)* *(Range: 2.9-141)*	5 years	23,000 ER visits ~6000 admissions	Increase in visits Same day – 1.80 1d lag – 2.90 2d lag – 2.64

* Study duration: length of time of study; is not equivalent to length of exposure

\+ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5A Epidemiology: Respiratory Health Effects Associated with Incremental Increases in Short-term Exposure to SO_2: Statistically Significant / Positive Findings (continued)

Exposure Increase ppb ($\mu g/m^3$)	*Effect*	*Baseline Exposure ppb* ($\mu g/m^3$)	Study Duration*	Study Population+	Reported Association
9.5 *(25)*	● Positive association with COPD emergencies in summer and winter[437]	------	~ 4 years	Daily mean emerg visits: Winter: 15.8 Summer: 8.3	COPD Increase: Winter: 6% Summer: 9%
9.5 *(25)*	● SO_2 increases associated with additional COPD admissions per day at different average daily SO_2 concentrations (27,38, and 57 ppb)[439]	24-hr mean: 21.6 ± 8.6 Range: 6.5-61 *(57 ± 23)* *(Range: 17-160)* 1-hr mean: 54.1 ± 37.7 Range: 5.3-274.8 *(142 ± 99)* *(Range: 14-720)*	~ 1 year	Daily mean visits: 11.9±5.6	24 hr average=38ppb 0.70/day (p<0.01) 24hr average=57ppb 0.55/day (p<0.01) 24hr average=27ppb 0.70/day (p=0.04)
10 *(26)*	◆ Increased lower respiratory symptoms in children from grades 2-5[426]	Effects only seen once ambient conc. >22ppb *(>57)*	1 year	1844 Subjects	OR 1.28 (95% CI 1.1 1.46)
15 *(39)*	◆ Increased lower respiratory symptoms in children with high BHR and serum IgE[605]	24hr mean: 3.2-8.6 *(8.4-23)*	3 winters (3 months each)	459 Subjects	Lag0 OR: 1.49 (95% 1.17-1.77) Lag1 OR: 1.28 (95%C 1.00-1.64) Lag2 OR: 1.58 (95%C 1.08-1.77) 5-day mean OR: 2.49 (95%CI 1.54-4.04)
19 *(50)*	◆ Increased risk of asthma attack incidence in children ages 7-10[448]	8.3 ± 5.2 Range: 1.7-32.0 *(22 ± 13)* *(Range: 4.5-84)*	25 weeks	Mild: 43 subjects Moderate: 47 subjects	Same day OR: 2.86 (9 CI 1.31-6.27) 1d Lag OR: 2.45 (95 CI 1.01-5.92)
19 *(50)*	◆ Association between daily mean and 1-hr SO_2 increase and hospital admission for COPD during warm season[369]	17.9 – 31.3 *(47-82)*	~ 5 – 12 years exposure	Admissions/d: 1.1 - 11	1-hr OR: 1.02 (95% 1.00-1.04) Daily OR: 1.05 (95% 1.01-1.10)
19 *(50)*	● Increased hospital admissions for respiratory disease in elderly patients (>65yrs) in New Haven and Tacoma[471]	New Haven mean: 29.8 *(78)* Tacoma mean: 16.8 *(44)*	~ 2 years	Mean admissions/d: New Haven: 8.8 Tacoma: 4.2	New Haven RR 1.0 (95% CI 1-1.13) Tacoma RR 1.06 (95 CI 1.01-1.12)

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Table 5A Epidemiology: Respiratory Health Effects Associated with Incremental Increases in Short-term Exposure to SO_2: Statistically Significant / Positive Findings (continued)

Exposure Increase ppb ($\mu g/m^3$)	*Effect*	*Baseline Exposure ppb ($\mu g/m^3$)*	Study Duration*	Study Population+	Reported Association
19 *(50)*	● Association with wheeze (5 and 6d lag), cough (6d lag) and shortness of breath (1wk lag) in asthmatic adults (mean age 46 yr)[455]	8.3 ± 5.2 Range 1.7-32.0 *(22 ± 13) (Range: 4.5-8.4)*	6 months	40 subjects	Wheeze 5d lag OR 1.35 (95% CI 1.01-1.81) 6d lag OR 1.44 (95% CI 1.08-1.92) Cough 6d lag OR 1.54 (95% CI 1.06-1.87) Shortness of Breath 1 wk lag OR 1.56 (95% CI 1.06-1.72)
19 *(50)*	● Increased emergency room visits for asthma in patients ages 5-34 yrs in 3 cities[409]	Daily mean 13.7 ± 9.6 *(36±25)* 15.0 ± 9.7 *(39±25)* 4.2 ± 3.2 *(11±8.4)*	~ 5 years	4416 subjects	Visit increase [illegible]
25 (in 5d mean) *(66)*	●Significant decrease in evening PEF -1.67 (-2.76 to -0.58) L/min, increase in phlegm and runny nose in asthmatic children[472]	Mean: 27.1 *(71)* Max.: 146.2 *(383)*	7 months	30 subjects	Phlegm OR 1.16 (95% CI 1.03-1.20) Runny Nose OR 1.07 (95% CI 1.04-1.10)
38 *(100)*	◆ Increase in asthma (5% significance) and acute respiratory disease (1% significance) admissions in winter[340]	Winter mean daily level: 13.0 ± 0.39 *(34 ± 1.0)*	~ 2 years	N/A	Asthma admission increase 4 (95% CI 0-7) Resp. disease admission increase 15.5 (95% CI 6-25)
IQR (?)	● Significant % decrease in morning PEFR in children (age 4-9 years) with asthma[432]	Average daily 53 Range 5-75 *(139) (Range 13-197)*	~ 1 year	Mean # of COPD Emergency Visits: [illegible]	OR= 1.48 per IQR (2-d lag)

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Table 5B Epidemiology: Respiratory Health Effects Associated with Incremental Increases in Short-term Exposure to SO_2: Insignificant / No Associations Found

Exposure Increase ppb ($\mu g/m^3$)	*Effect*	Baseline Exposure ppb ($\mu g/m^3$)	Study Duration*	Study Population+	Reported Association
1.7 *(4.5)*	● No association with morning or evening PEFR in COPD patients. Insignificant associations with eye irritation[470]	0-15 *(0-39)*	3 months	40 Subjects	Morning PEFR: 0.05% (95% CI -0.24 to 0.36%) Evening PEFR: -0.06% (95% CI -0.23 to 0.11%) Eye irritation RR: 1.17 (95% CI 0.99-1.38)
2.5 (8-hr) *(6.6)*	● No significant association with asthma symptoms considered "bothersome" or "more severe" on a 1d lag in children ages 10-16[413]	4.6 ± 3.0 Range: 1-20 *(12 ± 7.8) (Range: 2.6-52)*	3 months	22 Subjects	Bothersome OR: 1.11 (95% CI 0.97-1.28) More Severe OR: 0.91 (0.51 – 1.60)
3.5 *(9.1)*	● No association with hospital admissions and pneumonia in the elderly after a 2d lag[331]	4.8-6.6 *(13-17)*	~ 5 years	Respiratory mortality/d: Minnesota: 10.55 Birmingham: 8.26	Increase in admissions: 1.6% (95% CI -0.1% to 3.3%)
3.8 *(10)*	● No definitive association between SO_2 increases and respiratory, cardiac, cerebrovascular, and peripheral vascular diseases. Statistical significances were not reported[454]	5.4 *(14)*	~ 14 years	Total admissions: 449 278	2.8% excess daily hospital admissions ("completely explained by other variables")
3.8 *(10)*	● No significant association with hospital emergency visits for asthma[425]	24 hr = 10.2 *(27)* 1 hr = 21.5 *(56)*	~ 1 year	734 asthma cases	All CI included 1
3.8 *(10)*	◆ No association evident for exacerbation of symptoms in patients with COPD, regardless of lag or season[406]	Summer mean: 2.7 ± 1.9 Range: 0.8-10 *(7.1 ± 5.0) (Range: 2-26)* Winter mean: 7.3 ± 4.6 Range: 1.1-30.9 *(19-12) (Range: 2.9-81)*	14 months	39 Subjects	OR did not deviate significantly from 1

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Table 5B Epidemiology:. Respiratory Health Effects Associated with Incremental Increases in Short-term Exposure to SO_2: Insignificant / No Associations Found (continued)

Exposure Increase ppb ($\mu g/m^3$)	*Effect*	Baseline Exposure ppb ($\mu g/m^3$)	Study Duration*	Study Population+	Reported Association
3.8 *(10)*	◆ No association between asthma exacerbation and mean 24-hour increases, regardless of lag or season[402]	Summer mean: 2.7 ± 1.9 Range: 0.8-10 *(7.1 ± 5.0)* *(Range: 2-26)* Winter mean: 7.3 ± 4.6 Range: 1.1-30.9 *(19-12)* *(Range: 2.9-81)*	1 year	60 Subjects	All CI included OR=1
4.0 *(11)*	◆ No significant association with emergency visits for COPD for patients >14 yr, regardless of lag or season[431]	1-hr Mean: 21.5 Range: 3.4-60.1 *(56)* *(Range: 9-157)* 24-hr mean: 10.2 Range: 2.0-26.1 *(27)* *(Range 5.2-68)*	1 year	1298 COPD admissions	All RR were below 1 and were not statistically significant
4.0 *(11)*	◆ No significant association with daily hospital asthma admissions in Hong Kong or London, or respiratory disease admissions in London[423]	Hong Kong daily mean: 6.8 ± 4.7 *(18 ± 12)* London daily mean: 9.0 ± 4.7 *(24 ± 12)*	2 years	Avg. admissions/d: (Hong Kong/London) Asthma: 7.8/14.1 Resp.: 91.3/58.3 Cardiac: 98.7/121.1 IHD: 36.0/51.3	No statistically significant associations
4.0 *(11)*	● No significant associations wild mild asthma exacerbation (1d lag), and no association with moderate exacerbation for same day or 1d lag in children ages 10-16[413]	8-hr average: 7.0± 4.0 *(18 ± 10)*	3 months	22 subjects	Mild symptoms (1d lag) OR: 1.11 (95% CI 0.91-1.38) Moderate symptoms Same day OR: 1.37 (95% CI 0.87-2.18) 1d lag OR: 0.76 (95% CI 0.35-1.64)
5.7 (warm) *(15)* **7.8 (cool)** *(20)* **6.9 (all-yr)** *(18)*	● No statistical significance for any increased physician consults for respiratory disease in elderly, or young (0-14 yr) in warm season, or adults (15-64) in cool season or all-yr average[410]	7.8 ±2.5 (warm) *(20 ± 6)* 8.4 ± 3.4 (cool) *(22 ± 9)*	~ 2 years	Avg. daily consults: Young: 73.9±50.2 Adult: 96.3±62.6 Elderly: 15.5±11.3	3.5% change (95%CI 1.4%-5.8%)

* Study duration: length of time of study; is not equivalent to length of exposure

+ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5B Epidemiology: Respiratory Health Effects Associated with Incremental Increases in Short-term Exposure to SO_2: Insignificant / No Associations Found (continued)

Exposure Increase ppb *(μg/m³)*	*Effect*	Baseline Exposure ppb *(μg/m³)*	Study Duration*	Study Population+	Reported Association
6.8 *(18)*	● No association with % change in daily GP visits for asthma or lower respiratory disease in adults and elderly[469]	Mean daily (summer): 7.8 ± 2.5 *(20 ± 6)* (winter): 8.4 ± 3.4 *(22 ± 9)*	~ 2 years	Consults/d: (Asthma/other LRD) Young: 14.0/39.7 Adult: 17.8/73.8 Elderly: 3.6/41.4	Associations for adults and elderly independent of SO_2 concentrations
9.5 *(25)*	● No statistically significant association with hospital admissions or emergency visits for asthma in people > 14 yrs old[484]	Daily means: Summer: 40.8 *(107)* Winter: 52.0 *(136)*	460 d	N/A	No associations with SO_2 exposure
10 *(26)*	● No association with asthma hospital admissions in people <65 yrs old[482]	Mean daily: 8.0 *(21)*	~ 7 years	Admissions: 7837 asthma 6437 appendicitis	No associations with SO_2 identified
10 *(26)*	● No significant association with increased emergency admissions for cardiopulmonary ill health for a long study period and a short study period[473]	Mean daily: Long period: 14.5 ± 9.0 *(38 ± 24)* Short: 8.3 ± 5.6 *(22 ± 15)*	Short: ~3 years Long: ~14 years	All Cause Deaths/d: Short: 14.3 Long: 15.1±4.4	Short period: ≥65: CV: 4.9% (95% CI -1.0 to 11.0%) Resp.: -2.5% (95% CI -11.0 to 6.9%) ≤65: CV: -3.7% (95% CI -12.4 to 5.9%) Resp.: 0.0% (95% CI -8.3 to 9.1%)
10 *(26)*	● No significant association with asthma symptoms in children ages 5-12, regardless of lag period[462]	1-21 *(2.6-55)*	~ 2 years	133 Subjects	Same day OR: 1.07 (95% CI 0.90-1.27) 1d lag OR: 1.07 (95% CI 0.90-1.28) 2d lag OR: 1.00 (95% CI 0.83-1.20)
10 *(26)*	◆ Cough incidence not significantly associated with increased SO_2 for all concentrations, no significant association with upper respiratory symptoms, no significant association with lower respiratory symptoms at ambient concentrations<22 ppb[426]	Max. 24-hr average: 82 *(214)*. (cough incidence) Other effects investigated below 22 *(58)*	1 year	1844 Subjects	Cough incidence OR: 1.0 (95% CI 0.90-1.10)
19 *(50)*	◆ No significant association with all ages COPD symptom admissions[369]	1hr means: Amsterdam: 19 *(50)* Barcelona: 23 *(60)* Paris: 18 *(47)* Rotterdam: 31 *(81)*	~5 – 12 years	COPD Admissions: 1.1 - 11	OR 1.02 (95% CI 0.98-1.06)

* Study duration: length of time of study; is not equivalent to length of exposure

+ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5B Epidemiology: Respiratory Health Effects Associated with Incremental Increases in Short-term Exposure to SO_2: Insignificant / No Associations Found (continued)

Exposure Increase ppb *(µg/m³)*	*Effect*	**Baseline Exposure ppb** *(µg/m³)*	**Study Duration***	**Study Population⁺**	**Reported Association**
19 *(50)*	• Nocturnal cough (3 & 4d lag) not associated for entire study group. For asthmatics there was no association with wheeze and 1 week lagged SO_2[455]	Mean: 8.3 ± 3.2 Range: 1.7-32.0 *(Mean: 22 ± 8.4)* *(Range: 4.4-84*	6 months	40 Subjects	[illegible] 4d: [illegible] 3.40) Wheeze (asthmatics) 1.64 (95% CI 0.91-2.94)
50 *(131)*	• No statistically significant increase in hospital visits for asthma symptoms in children <16 yrs[385]	Mean: 70 Range: 10-490 *(183)* *(Range: 26-1284)*	~ 6 months	Population of children: ~450 000	[illegible] increase identified
51 *(134)*	• No statistically significant association with decreases in PEF in children (7-15yr) with asthma[435]	Range of means: 27.1-90 *(71-236)*	~ 2 years	257 Subjects	No statistically significant associations found
IQR (?)	• No effect on evening PEFR for children with asthma	Average daily 53 Range: 5-75 *(139)* *(Range: 13-197)*	~ 1 year	COPD Emergency visits d: 11.9±5.6	No association with evening PEFR

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* Study duration: length of time of study; is not equivalent to length of exposure

⁺ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5C Epidemiology: Respiratory Health Effects Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations – Positive/Statistically Significant Findings

Exposure Level ppb ($\mu g/m^3$)	Effect	Study Duration*	Study Population+	Reported Statistical Association
Summer: 1.65-3.97 *(4.3-10)* **Winter: 2.21-5.14** *(5.8-14)*	◆ Total respiratory admissions with and without asthma are correlated with summer SO_2 levels lagged 48 hours[367]	9 years Jan/Feb & Jul/Aug	Total admissions: Summer: 1 282 064 Winter: 1 223 456	Not reported
Low: 3.04 *(8.0)* **High: 4.94** *(13)*	● Significant association for asthma exacerbations with colds and levels of SO_2 which were significantly higher for a 3 day mean during warmer months[433]	~ 19 months	57 Subjects	$p<0.1$
Daily mean: 5.4 ± 3.0 Range 1.5-16.9 *(14 ± 8) (Range: 4 – 44)*	● Variation in clinic visits for lower respiratory tract illness is significantly associated with variations in SO_2 concentration[393]	1 year	Population at risk: 19 000 – 278 000	Not reported
Daily mean: 5.5 ± 5.7 *(14 ± 15)*	●For children aged 7 – 11 yrs, significant association between daily prevalence of cough and same-day SO_2 concentration. Significant association between previous-day SO_2 concentrations and lower respiratory symptoms[444]	3 consecutive winters	Winter 1: 308 subjects Winter 2: 381 subjects Winter 3: 390 subjects	Cough OR: 1.10 LRD OR: 1.18
Average daily means: 5.0 – 9.5 *(13 ± 25)*	● Hospital admissions for asthma associated with daily SO_2 levels in age groups 15-64 yrs and >64 yrs. Significant associations also seen for the control disease and pollutant levels[347]	2 years	2421 admissions	15-64: ($p=0.046$) >64: ($p=0.012$)
Daily mean: 7.3 ± 4.8 Range: 0.08-36.1 *(19 ± 13) (Range: 0.21-95)*	● Frequency of admissions for asthma (all age groups) were significantly correlated with daily levels of SO_2[453]	3 years	4209 admissions for asthma	7% more admissions during higher pollution.
Mean 1983 – 1987: 9.1 ± 3.1 *(24 ± 8)*	● Childhood asthma hospital admissions correlated with monthly and quarterly mean SO_2 concentrations[445]	~ 4 years	Population: 100 000 Asthma visits Emergency: 921 Clinic: 2183 ,	Month: $r=0.334$ ($p=0.01$) Quarter: $r=0.473$ ($p=0.07$)
> 15 *(39)* **Range of 24hr means: 6.5 to 6.8** *(17-18)*	◆ Increased SO_2 concentrations corresponded to decreased peak flow levels at concentrations above 15 ppb	8 months	27 nonallergic asthmatics aged 18-60 years from two cities	N/A
Peak hourly: Low: 20 – 40 *(52-105)* **High: 110 – 150** *(288-393)*	◆ Significant increases in eye and throat irritation, chest discomfort, shortness of breath, restricted activity, and medical visits during elevated pollution episodes compared to low pollution[011]	1 summer	1121 Subjects	Not reported
Peak concentrations: 24-hr: 40 *(105)* **1-hr: 56** *(147)*	◆ Winter air pollution events (elevated pollutant concentrations) associated with prevalence of wheeze and bronchodilator use, and decreased PEF in children with chronic respiratory symptoms[449]	1 winter	73 Subjects	Not reported

* Study duration: length of time of study; is not equivalent to length of exposure

+ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5C Epidemiology: Respiratory Health Effects Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations – Positive/Statistically Significant Findings (continued)

Exposure Level ppb ($\mu g/m^3$)	Effect	Study Duration*	Study Population+	Reported Statistical Association
Low: 40 *(105)* **High: >250** *(>655)*	◆ Patients age 55+ with grade 3 and 4 bronchitis, exposure to high SO_2 compared to low resulted in 50% greater person days of acute respiratory illness[010]	10 months	561 Subjects	Not reported
Means At least >57 *(149)* **Up to 171** *(448)*	● During first 13 weeks of study, correlation between SO_2 concentrations and children's respiratory morbidity. No clear exposure levels reported[428]	4 months	N/A	Not reported
0 – 190 *(0-498)*	◆ Increased prevalence of upper airway symptoms and nasal catarrh in exposed workers (n=136) versus controls. FEF_{25}, FEF_{50}, and FVC lower in subjects compared to controls[009]	"Years"	223 Subjects	Not reported
Average daily: 470 *(1232)*	◆ Smelter workers (n=36) had higher prevalence of dyspnea and lower baseline lung function compared to unexposed controls[016]	2 weeks	67 Subjects	Not reported

Table 5D Epidemiology: Respiratory Health Effects Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations– Statistically Insignificant Findings/No Associations

Exposure Level ppb ($\mu g/m^3$)	Effect	Study Duration*	Study Population+	Reported Statistical Association
Mean: Summer: 1.3 *(3.4)* **Winter: 2.6** *(6.8)* **24-hr range: 0.1-30** *(0.26-78)* **Maximal 1-hr: 50.0** *(131)*	● No association between frequency of registration of patients with acute asthma in an emergency department and concentration of SO_2[475]	~ 40 months	Population: 120 000 N=4127 asthma visits	No association
Low: 3.04 *(8.0)* **High: 4.94** *(13)*	● No association evident between asthma exacerbations with colds and daily levels of SO_2 in the colder months of the year, or with SO_2 concentrations 1-day before an event[433]	18 months	57 Subjects	No association
Daily mean: 5.5 ± 5.7 *(14 ± 15)*	● For children ages 7 – 11, no significant association between acute respiratory symptoms and SO_2 concentrations. SO_2 concentration not associated with pulmonary function[444]	3 consecutive winters	Winter 1: 308 subjects Winter 2: 381 subjects Winter 3: 390 subjects	No association
Average daily means: 5.0 – 9.5 *(13-25)*	● For 0-14 yr, no significant association between SO_2 level and hospital admissions for asthma[347]	~ 2 years	2421 total admissions	No association

* Study duration: length of time of study; is not equivalent to length of exposure

+ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5D Epidemiology: Respiratory Health Effects Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations– Statistically Insignificant Findings/No Associations (continued)

Exposure Level (ppb)	Effect	Study Duration*	Study Population+	Reported Statistical Association
Mean: 7.0 ***(18)***	● No association with asthma hospitalizations and SO_2 for boys aged 6 – 12 (all lag periods). No association for girls aged 6 – 12 for lag periods under 6d.[394]	~ 12 years	7319 asthma hospitalizations	No association
Mean 1983 – 1987: 9.1 ± 3.1 ***(24 ± 8)***	● No correlation between daily levels of SO_2 and asthma attack rates in children <10 yrs.[445]	~ 4 years	Population: 100 000 Asthma visits Emergency: 921 Clinic: 2183	No association
Daily levels: Low: 0 ***(0)*** **High: >10.9** ***(29)***	● No correlation between SO_2 daily maximums and prevalence of wheezing or any other symptoms in asthmatic schoolchildren[451]	1 year	99 Subjects	No association
Weekly mean: 3.8 – 24.5 ***(10-65)***	● Correlation between SO_2concentrations and ER visits for asthma in children investigated. No statistical significance calculated[485]	1 year	1076 Subjects	No association
Concentration range: 11 – 27 ***(29-71)***	● No significant association between SO_2 concentrations and incidence of respiratory symptoms in children aged 2 - 5[450]			No association
Annual Concentrations: Low: <15.3 ***(40)*** **High: 30.5** ***(80)***	◆ Exposure to higher concentrations of SO_2 not the cause of acute respiratory illness, when areas of low concentration exposure were compared to high[015]	3 years	4 Regions 240-280 families/region	No association
Median: 16 Range: 11-55	● A consistent, significant association between SO_2 exposure and peak expiratory flow was not observed[362]	4 months	60 asthmatic children	No association
Daily levels: 0 – 38 ***(0-100)***	◆ In children age 7 – 12, no association between prevalence of acute respiratory symptoms and concentrations of air pollutants during winter pollution episodes[018]	14 days	112 Subjects	No association
Range of daily averages: 0 – 38 ***(0-100)***	● No significant association with air concentration and total number of medical contacts for respiratory illness in children ages 0 – 15[457]	4 months	65 297 children 5307 contacts (3974 respiratory contacts)	p=0.68
Nonpolluted area: 13 – 27 ***(34-71)*** **Polluted area: 19 – 40** ***(50-105)***	● No correlation between SO_2 levels and total respiratory disease morbidity rates for all ages for pollution events in both the low and high polluted areas[006]	9 weeks/yr 3 years	Population base: 187 000	No association
Daily range: Rural: 1.3-24.8 ***(3.4-65)*** **Urban: 1.0 - 43.5** ***(2.6-114)***	● No clear associations with PEF, respiratory symptoms, or bronchodilator use in children aged 6 – 12[467]	2 months	Total Subjects 2010 14 studies – Avg pop/study: Urban: 50-91 Suburban: 60-84	No association

* Study duration: length of time of study; is not equivalent to length of exposure

+ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5D Epidemiology: Respiratory Health Effects Associated with Short-term Exposure to SO_2: Effects of Discrete SO_2 Concentrations or Comparisons of Concentrations– Statistically Insignificant Findings/No Associations (continued)

Exposure Level ppb (µg/m³)	Effect	Study Duration*	Study Population+	Reported Statistical Association
5-day average Mean: 73.4 ± 40 *(192 ± 014)* **Range: 14.7 – 275.5** *(Range: 39-722)*	● Changes in SO_2 concentrations are not associated with FEV_1 and MEFR in patients with COPD[342]	1 year	18 Subjects	No association
Mean hourly exposure: 150 – 660 *(393-1730)*	● Temporary work in a greenhouse at the reported high concentrations did not affect lung function[017]	6.6 years	42 Subjects	No association
Exposures up to 610.6 *(1600)*	● No significant correlation between PEF on arrival at work each day and pollution index[031]	Up to 2 years	4 Subjects	No association
Exposures of 0 – 1500 *(0-3931)*	◆ No significant correlation between SO_2 and asthma emergency room visits, despite comparisons of results on a daily, weekly, and monthly basis[023]	1 year	854 Emergency visits	No association
Plant 1: 1030 *(2700)* **Plant 2: 200 – 1800** *(524-4720)*	● Causative role of exposure and irritative effects in cement plant workers undetermined[26]	Plant 1: 5-6 months Plant 2: 6-8 months	N/A	No association
Up to 2135.0 *(5595)*	● No significant associations with FEV_1, FVC, and MMEF in 4 subjects[029]	5 years	4 Subjects	No association
Range of exposures: 5- minute block mean: 0 – 3319 *(0-8698)*	◆ No evidence of any positive relation between peak SO_2 concentrations and hospital presentations or admissions for asthma, wheeze, or shortness of breath[007]	3 years	N/A	No association
Ambient concentration (?)	● In our subjects, no clear association between SO_2 concentrations and changes in spirometric tests[030]	5 years	4 Subjects	No association
Not given	● Pearson correlation coefficient between SO_2 levels and respiratory visits was negative.[475]	1 year	28 471 patients	No association

* Study duration: length of time of study; is not equivalent to length of exposure

+ Study population: the definition of study population is different for each study and ranges from the populations of the city(ies) in which the study was conducted to hospital admissions for the health outcome of interest.

Table 5E Epidemiology: Respiratory Health Effects Associated with Increases in Short-term Exposure to SO_2: Statistically Significant / Positive Findings – *Protective Effect*

Exposure Increase ppb (mg/m^3)	Effect	Baseline Exposure (ppb)	Study Duration*	Study Population+	Reported Association
38 ***(100)***	● Statistically significant protective effect against hospital admissions for asthma for adults >65[353]	24 Hour mean: Amsterdam: 11 Rotterdam: 15	12 years	Respiratory admissions/d: 6.7	RR: (0.802 – 0.995)

Table 6. Respiratory Health Effects Associated with Short-term Exposure to SO_2 Summary of "Positive" Findings: Clinical and Non-clinical studies

Concentration (ppm)	Effects
0.03	◆*More rapid and more severe inflammatory response to influenza infection (to 0.1 ppm; Mice)*[illegible]
0.1	▲*Increased respiratory pause (Guinea pigs)*[illegible] ◆Slight reduction in FEV_1, $V_{max\ 50}$ (AC)[illegible] ◆Bronchoconstriction at lower concentrations in dry air than humidified air (HA)[illegible] ◆*Slight reduction in lung clearance (Rats)*[illegible] ◆*Increased antigen-specific antibodies in serum and bronchoalveolar fluid (Guinea pigs)*[illegible]
0.15	◆Decreased specific airway conductance (HA)[illegible]
0.2	◆Increased respiratory frequency (AA)[illegible] ●Bronchoconstriction (AA)[illegible]
0.25	◆Increased SRaw (AA)[illegible] ◆Increased bronchoconstriction(AA)[illegible]
0.3	◆Increased bronchoconstriction, returned to normal levels 30 min. post-exposure (and 0.6 ppm; AA)[illegible]
0.5	▲Increased SRaw (AA)[081,109] ▲Dose-dependent change in respiratory function (to 1 ppm; AA)[illegible] ▲*Dose-dependent increases in lung resistance (and 5 ppm; Rabbits)*[illegible] ◆Reduction in FEV_1, $V_{max\ 50}$, V_{max75} (AC)[099], (AA)[055] ◆Dose-dependent effect on FEV_1, $V_{max\ 50}$, V_{max75} (to 1 ppm; AA)[illegible] ◆Increased SRaw (AA)[061], greater with oral than nasal exposure (AA)[074]; with cold dry air (AA)[illegible] ◆SO_2 responsiveness decreased with opioid and increased with cyclooxygenase inhibitor (to 8 ppm; AA)[052] ◆Dryness, irritation, or burning of the throat (to 5 ppm; HA)[039] ◆Chest tightness, wheezing, dyspnea (and 1 ppm; AA)[064] ◆Increased bronchoconstriction(AA)[326] ●Changes in AM and BM chemotactic activity[illegible]
0.60	◆Decreased respiratory function (AA)[304,314] ●Bronchoconstriction[376] ●Increased SRaw(AA)[30]
0.75	▲Increased SRaw (HA)[060] ◆Reduction in FEV_1, increased total respiratory resistance (AC)[10] ◆Increased SRaw initially, decreased to pre-exposure levels after 1 hr of exposure (AA)[illegible] ◆Increase SRaw with hyperventilation[318] ◆Increased SRaw[304] ●Increased prevalence of compound cilia (HA)[046]
<1	Chest tightness, wheezing, dyspnea, cough (AA)[093]
1 ppm	▲Decreased spirometric function (HA)[096] ◆Reduction in FEV_1, $V_{max\ 50}$, V_{max75} (AC)[038,102], (AA)[illegible] ◆Slight reduction in FEV_1, $V_{max\ 50}$, V_{max75} or increased bronchoconstriction after exercise (HC)[illegible] ◆Increased SRaw (HA)[047], (AA)[062,064,078] ◆Decreased nasal mucous flow rate (HA)[063] ◆Decreased $MEF_{50\%VC}$ (HA)[070] ◆Discomfort proportional to SO_2 concentration (to 25 ppm; HA)[illegible] ◆Functional impairment of alveolar macrophages (to 5.0 ppm)[308] ◆*Increased respiratory resistance; decreased compliance (Guinea pigs)*[illegible] ◆*Dose-dependent increase in bronchoconstriction (to 2.5 ppm; Guinea pigs)*[illegible] ◆*Decreased proportion of macrophages in white cells (to 5 ppm; Guinea pigs)*[illegible] ●Threshold for bronchoconstriction (10 breaths;HA)[illegible] ●Decreased tidal volume, increased respiratory rate (HA)[illegible] ●Increased SRaw returning to control values post-exposure (HA)[illegible] ●Changes in SRaw[324] ●*Increased bronchial sensitivity (Dogs)*
1.4	●*Increased intranasal transport time (Chickens)*[illegible]
1.5	●*Increased airway resistance (to 26 ppm; Guinea pigs)*[illegible]
2	◆Changes in SRaw (AA)[062,303] ◆Difference in ventilatory parameters between forced oral and free-breathing exposures (HA)[illegible] ●*Increased bronchial constriction (to 1000 ppm; Guinea pigs)*[illegible]

Table 6. Respiratory Health Effects Associated with Short-term Exposure to SO_2 Summary of "Positive" Findings: Clinical and Non-clinical studies (continued)

Concentration (ppm)	Effects
2.5	◆Decreased specific airway conductance greater with oral than nasal exposure (HA)[105] ◆Dose-dependent increase in ciliary beat frequency (to 12.5 ppm)[320,427] ●Dose-dependent decrease in ciliary beat frequency (12.5 ppm)[466] ●*Decrease in mucociliary activity (Guinea pigs)*[164] ●Decreased specific airway conductance (to 20 ppm; AA)[092]
3	●*Dose-dependent decrease in mucociliary activity (to 14 ppm; Guinea pigs)*[132]
3.4	◆*Increased incidence of pneumonia after exposure to SO_2 (to 34.5 ppm; Mice)*[182] ●*Increase in mononuclear and polymorphonuclear cells and number of plasma cells (to 18.5 ppm; Chickens)*[199]
4	◆Increased alveolar activity in BAL (and 8 ppm; HA)[083] ◆*Increased airway reactivity in asthmatic sheep 24 hr after exposure (Sheep)* [230] ●Decreased airway conductance and thoracic gas volume (HA)[069] ●Increased pulmonary flow resistance (HA)[076] ●Dose-dependent increase in mast cells, lymphocytes, macrophages in BAL (up to 8 ppm)[091] ●*Increased nasal turbinate clearance time (Chickens)*[138]
5 ppm	◆Decreased MMFR, increased bronchial clearance (HA)[045,056] ◆Decreased nasal mucous flow rate (HA)[048] ◆SRaw exhibited in all subjects[375] ●Increased bronchial reactivity (AA)[084] ●Decreased FEV_1 (to 11.5 ppm; AA)[108] ●Increased SRaw[416] ●*Dose-dependent decreased in ciliary beat frequency (to 12.5 ppm; Guinea pigs)*[164] ●*Dose-related increase in electrophoretic bands from nasal mucous (to 20 ppm; Rats)*[193]
6	◆*Inhibition of virus growth (Mice)*[238] ●*Decreased mucociliary transport rate (Chickens)*[149] ●*Decreased nasal mucous elastic recoil distance in vivo (Chickens)*[149]
7	●*Increased nasal and pulmonary flow resistance (to 230 ppm; Dogs)*[170]
8	▲*Increased lipid peroxide formation in lungs (Rats)*[171] ◆The effectiveness of atropine in controlling bronchoconstriction decreased as a subject's SO_2 responsiveness increased (HA,AA)[059] ◆Increases in macrophages, lymphocytes, and mast cells in BAL (HA)[090] ●Increased SRaw (AA)[116]
10 ppm	◆Bronchial obstruction, returned to control by 45-60 min. post-exposure (AA)[260] ◆*Increased airway reactivity in asthmatic sheep 24 hr after exposure (Sheep)* [231] ◆*Lesions of olfactory and respiratory epithelium (Mice)*[191] ◆*Increased concentrations of cholesterol, total lipids, gangliosides and decreased phospholipids (Guinea pigs)*[163] ◆*Decrease in thickness of olfactory mucosa, severe rhinitis (Mice)*[191] ◆*Inhibition of ciliary movement (Rabbits)*[468] ●*Ciliary movement stopped when SO_2 blown directly onto trachea (Rabbits)*[417] ●*Increased lung hypersensitivity to aerosolized methacholine (Dogs)*[258]
11	●*Bronchoconstriction (to 1000 ppm; Dogs)*[167]
15	◆Increased pulmonary flow resistance; greater from oral than nasal exposure (HA)[054] ◆*Dose-dependent increased in ciliary activity (to 77 ppm; guinea pigs)*[213]
16	◆SO_2 absorbed in upper respiratory tract (HA)[033]
17	◆*Dose-dependent respiratory depression (to 298ppm; Mice)*[243]
18	●*Decrease in turbinate clearance (Chickens)*[137]
20	◆*Delayed early clearance of upper respiratory tract (Rats)*[256] ●*Sneezing, rubbing eyes and noses (to 330, Guinea pigs)*[142] ●*Increased pulmonary flow resistance (Cats)*[290] ●*Edema, loss of cilia, epithelial thinning (Mice; 60 to 120 minutes)*[287]
27	●*Decrease in lung clearance (Hamsters)*[134]
40	◆*Dose-dependent decrease in % SO_2 retention, respiratory rate, minute volume, increase in tidal volume (Rats)*[253] ●*Epithelial damage in large airways (Hamsters)*[198] ●*Increase in static lung compliance (Mice)*[208]
50	▲*Reduction in pulmonary macrophage endocytosis(Hamsters)*[374] ◆*Reduced dynamic compliance (Dogs)*[189]

Table 6. Respiratory Health Effects Associated with Short-term Exposure to SO_2 Summary of "Positive" Findings: Clinical and Non-clinical studies (continued)

Concentration (ppm)	Effects
100 ppm	▲*Increase in minute volume (Chickens)* ◆*Decreased glutathione concentration and inflammation (Rats)* ●*Dose-dependent increase in lung resistance (to 1000ppm, Cats)*
150	◆*Increased lung resistance, decreased breathing frequency (Rabbits)*
200	◆*Decreased breathing frequency, increased tidal volume (Rabbits)* ●*Increased inspiratory and decreased expiratory time (Rabbits)* ●*Increased airway hyperreactivity (Dogs)* ●*Decrease in mechanically stimulated cough reflex (Rabbits)*
230	●*Increased numbers of polymorphonuclear leukocytes in tracheae(Rats)*
300	●*Increased inspiratory and expiratory time (and 350 ppm; Rabbits)* ●*Increased acid phosphatase and β-glucuronidase and β-galactosidase activities (Rats)*
350	●*Decreased glycoprotein concentrations (Chickens)*
400	●*Increase in bronchial response to histamine (Dogs)*
500	▲*Decreased SRaw(Chickens)*[183] ◆*Changes to bioelectric properties and increased nonelectrolyte permeability (Dogs)* ●*Changes in lung lipids and membrane permeability (Squirrels)*
600	◆*Increased mucosal permeability (Rats)*[70] ◆*Increase in solid material recovered by bronchial lavage (Rats)* ●*Acute bronchitis, bleeding of rhinopharynx, chronic tracheobronchial injuries (Rats)*
627	●*Decreased surface forces and transpulmonary pressures (Rats)*
800	◆*Reduction in minimal and maximal pulmonary surface tension (Rats)* ◆*Gradient of decreasing damage in the tracheobronchial tree(Rats)* ●*Loss of epithelial cells and increased permeability (Guinea pigs)*
1000 ppm	▲*Initial decrease then increase in SRaw, increased respiratory frequency, decreased minute volume (Chickens)*[183]
1225	◆*Pulmonary edema, greater reduction in surface tension (Rats)*
2500	●*Edema found in the separation of the surface epithelium from the alveolar septum (to 4000 ppm, Rats)*
3000	●*Reduced tidal volume, increased respiratory frequency and pulmonary resistance (to 7000 ppm, Cats)*

Table 7. Respiratory Health Effects Associated with Short-term Exposure to SO_2 Summary of "Negative" Findings: Clinical and Non-clinical studies

Concentration (ppm)	Effects
0.20	◆No effect on respiratory function in asthmatic adults [067]
0.4	◆Normal respiratory function in healthy adults [049,051]
0.5	▲No bronchoconstriction in healthy adults[073] ▲Normal respiratory function in asthmatic adults (and 0.25 ppm)[075]
0.60	◆No effect on healthy adults[309]
0.75	▲No effect on respiratory function in healthy adults [043]
0.8	◆No effect on respiratory function in asthmatic adults [101] ◆*No effect on respiratory function in guinea pigs* [204]
1 ppm	◆No effect on respiratory function in healthy adults [040,112,306] ◆*No effect on respiratory function in guinea pigs* [257]
2	◆No effect on respiratory function in healthy adults [266] ◆No signs or symptoms observed in healthy adults[072] ◆*No biochemical changes observed in rat lungs*[225] ●*No effect on respiratory function in guinea pigs* [226]
3.3	◆No relationship between peak ambient SO_2 and hospital presentations or admissions for asthma[007] **?**
3.6	◆No effect on respiratory function (from 1.1 ppm) in healthy adults [113]
4	●No effect on respiratory function in healthy adults [087]
5	◆No effect on respiratory function in healthy adults (from 0.5 ppm) [039]
10 ppm	
15	●No effect on FEV_1 in healthy adults[108]
20	●No effect on specific airway conductance in healthy adults (from 2.5 ppm)[092,325]
46.5	◆*No changes in pulmonary benzo(a)pyrene metabolism observed in rat lungs*[252]
50	●*No effect on water or histamine content of guinea pig lungs (and 10 ppm)*[126] ●*No significant changes in material in bronchoalveolar lavage fluid (Rats)*[447]
89	●*Few signs of respiratory distress in guinea pigs*[125]
100 ppm	◆*No change in bioelectric properties in dogs*[150]
300	●*No respiratory effects in donkeys (from 35 ppm)*[262] ●*No respiratory effects in rabbits (from 200 ppm)*[161]
700	●*No increased sensitivity to acetylcholine challenge (and 450, 600 ppm)*[144]
713	●*No respiratory effects in miniature donkeys (from 27 ppm)*[205]

Table 8. Non-respiratory Health Effects Associated with Short-term Exposure to SO_2
Summary of "Positive" Findings: Clinical and Non-clinical studies

Concentration (ppm)	Effects
0.01	◆Eye irritation reported in the general population during periods of high and low pollution up to 0.11 ppm[080]
0.03	◆*Antibodies to virus developed more rapidly and increased number of goblet cells in mice exposed up to 0.1 ppm for 4 weeks*[20]
0.1	▲*Enhanced ovalbumin-induced asthmatic reactions in guinea pigs exposed 5 hours/day for 5 days*[20] ◆*Increased blood pressure and heart rate observed in geese exposed to up to 400 ppb for 1 to 3 minutes*[20] ◆*Increased ovalbumin-specific antibodies and bronchoalveolar fluid in guinea pigs exposed to up to 16.6 ppm for 8hours/day, 5 days*
0.2	◆Differences in "total cardiac power" observed in healthy subjects exposed for 1 hour[07]
0.3	●Positive correlation between plasma S-sulfonate and atmospheric SO_2 in healthy smokers and non-smokers exposure to up to 6 ppm for up to 120 hours[20]
0.4	●Throat irritation and unpleasant smell reported in healthy adults exposed to between 0.4 and 4 ppm for 20 minutes[08]
0.5	▲Symptoms of decreased lung function with increased SO_2 concentration up to 0.5 ppm[20] ◆7 of 8 asthmatic subjects reported wheezing and chest tightness after 3 and 5 minutes of exposure[20]
0.75	◆Increased asthma symptoms reported in adults after 10 minutes of vigorous exercise during exposure[079]
0.87	◆*Decreased whole blood and packed cell viscosities after 24 hours exposure (Rats)*[07]
<1	◆Increased chest tightness, wheezing, cough, dyspnea in asthmatic subjects and taste and odour complaints from healthy subjects with increased SO_2 concentration during a 40 minute exposure[20]
1 ppm	▲Increased nose and throat irritation in healthy adults after exposure for 4 hours/day, 3 days/week for 3 weeks[096] ▲Shortness of breath, and chest discomfort in asthmatic subjects after 10 minutes of exposure[20] ◆Shortness of breath and wheezing reported in asthmatic children exposed for 30 minutes at rest and 10 minutes of exercise[041] ◆Discomfort proportional to SO_2 concentration reported in healthy adults exposed to up to 25 ppm SO_2 for 6 hours/day for 3 days[063] ◆2 of 8 asthmatic subjects reported chest tightness after 1 minute of exposure[064] ●Objective odours, irritation of the upper respiratory tract and unusual sensations in the lung reported by healthy adults exposure to between 1 and 60 ppm for 5 minutes[053]
1.8	●*Low, uniform $^{35}SO_2$ concentration in heart muscle, high concentration in kidney, and low concentration in liver in dogs after exposures up to 148 ppm for 30 to 40 minutes (Dogs)*[11]
3	●Dose-dependent, reversible eye response observed in healthy adults exposed to between 3 and 60 ppm for 1 second[121]
3.4	●*Increased number of macrophages, lymphocytes, plasma cells and neutrophils in chickens exposed to up to 18.5 ppm for 1 to 14 days*[199]
4	◆Dose-dependent increased in macrophage activity 24 hours post-exposure up to 8 ppm in healthy adults[083] ●Increased macrophage activity in healthy adults 24 hours post exposure up to 11 ppm for 20 minutes[091]

Table 8, continued. Non-respiratory Health Effects Associated with Short-term Exposure to SO_2
Summary of "Positive" Findings: Clinical and Non-clinical studies

Concentration (ppm)	Effects
5	▲*Dose-dependent increase in plasma and liver triglycerides and HDL cholesterol in normal and hypertensive rats and decrease in plasma triglycerides, liver triglycerides and liver weight and increased in HDL cholesterol in diabetic rats exposed for up to 10 ppm for 15 days*[152] ▲*Changed behaviour in mice after exposure to up to 30 ppm for 24 days*[214] ◆50% decrease in nasal mucous flow in healthy adults after 4 hours of exposure[048] ◆*Changed behaviours in adult mice after prenatal exposure to up to 30 ppm for 14 days*[217] ◆*Decreased glutathione and varied enzyme activity observed in the hearts, liver, lung, and kidneys of rats exposed to up to 100 ppm for 5 hours/day for 7 to 28 days*[251] ●Threshold for tear production for 15 second exposure in humans[121] ●*10% of inhaled SO_2 found in blood or plasma within first 30 minutes of exposure (up to 20 ppm; Rats)*[193] ●*Increased frequencies of polychromatic erythrocyte formation (Mice)*[380]
6	◆*Inhibition of influenza virus growth in mice exposed for 7 days*[238] ●*Increased hemoglobin at all concentrations up to 310 for 60 minutes exposure (Guinea pigs)*[254]
10 ppm	▲*Increased mortality rate, decreased survival time (Mice)*[172] ▲*Decreased total lipids and free fatty acids, nasopharyngitis, somnolence, staggering, itching, preening, skin and eye irritation observed in guinea pigs exposed for 1 hr/day for 21 days*[159] ◆*Increased cholesterol, total lipids, phospholipids and decreased gangliosides observed in the hearts and other organs of guinea pigs exposed for 1 hour/day for 30 days*[163] ◆*Increased methemoglobin, sulfhemoglobin, lipoperoxidation and osmotic fragility, and decreased phospholipids and cholesterol after exposure for 1 hour/day for 30 days (Guinea pigs)*[236] ◆*Lipid content and enzyme activity vary depending on brain area in rats after one hour of exposure per day for 30 days*[249]
15	◆Coughing and burning sensations in the throat and substernal area reported by healthy adults exposed to 15 and 28 ppm for 10 minutes[054]
19	●*Inorganic sulphur in blood at concentrations up to 310 ppm at 60 minute exposures (Guinea pigs)*[254]
20	◆*Decreased liver catalase activity (Rats)*[381]
23.5	●*Increased plasma and serum S-sulfonate levels in rabbits exposed for 14 to 62 hours*[222]
25	◆*Decreased mean fetal body weight, delayed ossification of sternebrae and occipital bone after exposure on gestational days 6 to 15 (Mice)*[140]
40	◆*Reversible effects such as depressed feed and water intake, decreased body weight, and O_2 consumption observed in mice exposed to 4 to 11 days*[261] ◆*Decreased plasma thyroxine levels at 12 and 24 hours exposure; increased plasma glucocorticoids at 1 and 12 hours (Mice)*[212]
50	●*Decreased blood pressure in hypertension-resistant rats and increased blood pressure in other rats exposed to 6 hours/day, 5 days/week, for 6 weeks*[241]
65	◆*Decreased pup weight in mice after exposure to 65 and 125 ppm during gestational days 7 to 17*[203]
70	◆*Minor skeletal variations in rabbits after exposure on gestational days 6 to 18*[140]
100 ppm	
200	●*Increased airway permeability to plasma proteins and cell shedding in dogs exposed for 2 hours*[146]
250	◆*Increased uptake of Fe in airway epithelium after 3 hours exposure (Mice)*[209]
330	●*Hematoglutination observed in 5 of 10 guinea pigs exposed for 30 minutes*[142]
400	●*3 of 30 exposed rats died in the first 5 hr of exposure, 22 of the remaining 27 died in the first week of exposures for 5 hr/day, 5 days/week*[198] ●*Some signs of irritation observed in guinea pigs exposed for 30 minutes*[143]
500	●*Decreased lipid levels and increased moisture content in squirrel hearts after 4 minute exposure*[147]
590	●*Decreased survival time with increasing concentration up to 500,000 ppm (Rats)*[218]
900	◆*% mortality rate increased with increased exposure time from 10 to 640 min (Mice)*[174]
1000 ppm	▲*2 of 10 chickens died at 60 min exposure*[183]
1400	◆*% mortality rate increased with increased exposure time from 10 to 640 min (Mice)*[174]
1900	◆*% mortality rate increased with increased exposure time from 10 to 640 min (Mice)*[174]
5000	▲*Decreased blood pH and O_2 and increased blood CO_2 in chickens exposed for 60 minutes; 9 of 10 chickens died at 60 min exposure*[183]

Table 9. Non-respiratory Health Effects Associated with Short-term Exposure to SO_2
Summary of "Negative" Findings: Clinical and Non-clinical studies

Concentration (ppm)	Effects
0.15	◆No signs or symptoms of irritation in health adults after exposure for 2 hours[055]
0.25	▲No signs or symptoms of irritation in asthmatic adults after exposure up to 0.5 ppm for 1 hour[055]
0.4	◆No signs or symptoms of irritation in asthmatic adults after exposure up to 1 ppm for 1 hour[055]
0.5	◆No correlation between plasma antioxidant concentrations and sensitivity to SO_2 in asthmatic adults exposed for 10 minutes[055]
0.95	◆*No change in mortality rates in mice exposed for 2 hours*[134]
1 ppm	▲No adverse eye effects observed in healthy adults exposed for 4 hours/day, 3 days/week for 2 week[096] ●*No significant effects on hemoglobin concentration (Rats)*[134]
2	◆*No hematopoietic effects observed in rats exposed for up to 49 days*[134]
3.3	◆No association between peak SO_2 concentrations and hospital presentations of admissions for asthma, wheeze or shortness of breath up to 3.3 ppm[001]
8	●No effect observed on the cardiovascular system of healthy aduults after exposures between 1 and 8 ppm for 10 minutes[031]
10 ppm	
27	●*No difference in bacterial clearance rates in hamsters exposed for an undetermined amount of time*[134]
30	▲*No changes observed in reproductive performance or neurobehavioural development of offspring in mice exposed to up to 30 ppm from 9 days pre-pregnancy to gestational day 12-14*[134]
40	●*No increased mortality in rats or hamsters with gradually increasing concentrations up to 400 ppm*[134]
50	●No subjective eye effects reported by healthy adults exposed for 5 minutes[096]
100 ppm	▲*No cardiovascular or hematopoietic effect on chickens during a 1 hour exposure*[134]
250	◆*No effect on number of dead or reabsorbed fetuses, no teratological effects in mice exposed to 32 to 250 ppm from gestational days 7 to 17*[134]
300	●*No signs of irritation in guinea pigs at concentrations lower than 300 ppm for a 30 minute exposure*[134]
5000	◆*No change in blood pressure in rats exposure for 2 breaths*[134]

APPENDIX 1

TITLES AND AFFILIATIONS OF THE EXPERT PANEL

APPENDIX 1: TITLES AND AFFILIATION OF THE EXPERT PANEL

Randy P. Angle, PhD
Section Head
Air, Science & Standards Branch
Environmental Assurance Division, Alberta Environment

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Medical Toxicologist, Alberta Poison Centre
Calgary Health Region

APPENDIX 2

MEMBERS OF THE REVIEW TEAM

APPENDIX 2: MEMBERS OF THE REVIEW TEAM

James Andruchow, M.Sc.

Lorelei Betke, M.Sc.

Michael Lam, Ph.D.

Norah Lee, M.Sc.

Rabindra Mahabeer, B.Sc.

Christine Teixiera, Ph.D.

Corinna Watt, M.Sc.

APPENDIX 3

SEARCH STRATEGY

APPENDIX 3: SEARCH STRATEGY

	Inclusion/Exclusion terms:	Number of documents identified:
1. TITLE or KEYWORDS must INCLUDE at least one of the following terms:	SO2; sulphur dioxide; sulfur dioxide; sulphur oxides; sulfur oxides	23499
2. From the list generated by (1), INCLUDE documents with any of the following terms in the TITLE or KEYWORDS:	Acute' subacute; short term; accident; case stud-; toxic; adverse; neurology-; CNS; central nervous system; nervous; brain; behaviour; clinical; teratol-; teratogen; embryotox; reproduct-; development; pregnan-; fetus; fetal; birth defect; chamber; respir; pulmonary; lung; asthma; irritant; airway; ocular; eye; trachea; nasal; bronch	6803
3. From the list generated by (2), EXCLUDE documents with any of the following terms in the TITLE or KEYWORDS	Cancer, Carcinogen, Tumour; Tumor; Neoplas-; Oncogen; Adenoma; Malignan-; Genotox; Mutat-; Mutagen; Cytogen; Clastogen; DNA repair; Aquatic; Marine; Benthic; Fish; Invertebrate; Cataly-; Computer; Treatment; Rain; Ecolog-; Magnesium; Mortality; Pine; Preservative; Kinetics; transport; deposition; lake; soil; bacteria; food, additives; economic; admission; distribution; aberrations; chroma-; calibrat-; pharmacokinetics; conversion; soil; precipitation; agriculture; woody; stability; crop; measurement; leaves; tree; forest; soybean; grass; algae; lichen; selenium	6802
4. From the list generated by (3), EXCLUDE documents with any of the following terms in the TITLE:	Air pollution; pulp mill; paper mill; ambient; vegetation; ecosystem; spectrophoto-; photosynthesis; occupational; fumigat-	3133
5. From the list generated by (4), ISOLATE by publication language:	English only	2468

APPENDIX 4: REVIEW FORMS

A. CLINICAL

B. NON-CLINICAL

C. EPIDEMIOLOGY

CLINICAL REVIEW FORM

Author:	**Internal ID:** ID of study within database
Title:	
Year:	
Abstract:	
Objective: The authors' stated objective and identification of relevant experiments in documents reporting findings from multiple studies.	

Overall study design:

Exposure level	Exposure frequency/duration	Gender	Age	Number of subjects	Pre-trial health	NOAEL	LOAEL
						No observed adverse effect level	Lowest observed adverse effect level

Observations:

Reported data
*Statistically significant

Author's Conclusions:

Quotations of the author's primary conclusions

Review – Assessment: [NB: In actual reviews ! is replaced by: (+) denoting compliance with guidelines, (-) denoting a diversion from guidelines or (+/-) denoting a characteristic which is neither positive nor negative but is worthy of mention.]

A. Subjects:	✍ Is the number of subjects sufficient to produce statistically significant results? ✍ Are characteristics (e.g., age, sex, health, work history, medical history) of test subjects adequately recorded and appropriate for the objective of the study? ✍ Are the subjects a representative sample of the population to which extrapolations will be made? ✍ Was the method of recruitment appropriate? Would the participation incentive employed cause the selection of an unrepresentative sample population? ✍ Were subjects informed about the experimental risks? Was this information provided in such as a way as to prevent bias?

B. Exposure conditions:	✎ Was a full description (manufacturer, purity, lot no.) of the reagents used in the trial provided? ✎ Was there a gradient of exposure levels? ✎ Were the chosen exposure levels appropriate to investigate the primary objective? ✎ Were previous preliminary trials conducted to identify the range of appropriate exposure levels? ✎ Were both nominal and actual exposure concentrations recorded? ✎ Was the duration of exposure appropriate to investigate the primary objective? ✎ Was the duration of exposure precisely defined? ✎ Was the mode of administration appropriate? ✎ Was the frequency of administration appropriate to investigate the primary objective? ✎ Was evidence provided to justify the dosing regime? ✎ Were exposure concentrations, airflow, temperature, and humidity monitored continuously?
C. Equipment:	✎ Was information pertaining to the type, dimensions, material and atmospheric pressure of the exposure device outlined ✎ Was a full description of the monitoring devices provided? ✎ What was the sensitivity of the monitoring devices employed?
D. Procedural:	✎ Were the subjects randomly assigned to exposure groups? ✎ Was the method of randomization defined? (*i.e.,* information pertaining to the mechanism used to generate random assignment) ✎ Was a control group assayed? ✎ Is the control regime appropriate? ✎ Was the type of blinding indicated? (*i.e.,* single, double, triple, etc) ✎ Was the length of follow-up appropriate? ✎ Was the nature of follow-up appropriate? (*i.e.,* questionnaire, interview, medical exam, etc)
E. Data collection:	✎ Were appropriate endpoints examined? ✎ Was the assessment thorough? (*i.e.,* information pertaining to the clinical nature, duration, reversibility, severity, onset and dose-response relationship provided for each symptom) ✎ Were accepted assessment methods employed? ✎ Were assessment measures sufficiently sensitive? ✎ Was the nature and severity of symptoms graded against an explicitly defined scale? ✎ Did qualified personnel conduct the exams? ✎ Was the timing and frequency of assessment logical? ✎ Was raw data provided to permit the reader to arrive at his/her own conclusions? ✎ Was individual data reported for each subject? ✎ Are all withdrawals listed, with the reason for withdrawal?

F. Data analysis:	✎ Are the statistical methods used appropriate? ✎ Are confidence intervals reported? ✎ Did the investigator appropriately interpret the statistics? ✎ Are the observed trends statistically significant?
G. Interpretations:	✎ Was the original objective addressed? ✎ Are the results novel? ✎ Was the design of the study appropriate to investigate the primary objective? ✎ Were assumptions reasonable? ✎ Are the methods reproducible? ✎ Did either the study design or the statistical analysis limit confounding variables? ✎ Do the conclusions make biological sense? ✎ Are the extrapolations reasonable? ✎ Is the paper in a peer-reviewed journal? ✎ Would either the affiliation of the investigative team or sponsor potentially bias the conclusions reached in the document?

Review - Summary:

Discussion of findings:
Reviewer's summary of study findings and interpretation of the toxicological significance and clinical relevance of these findings.
Confidence index:
Reviewer's assessment of the quality of the study design, conduct and reporting.

Review – Confidence index ranking:

High
High to moderate
Moderate to high
Moderate
Moderate to low
Low to moderate
Low

NON-CLINICAL REVIEW FORM

Author:	**Internal ID:** ID of study within database
Title:	
Year:	
Abstract:	
Objective: The authors' stated objective and identification of relevant experiments in documents reporting findings from multiple studies.	

Overall study design:

Exposure level	Exposure frequency/duration	Species	Strain/ Breed	Age	Sex	Number of animals	Pre-trial health	NOAEL	LOAEL
								No observed adverse effect level	Lowest observed adverse effect level

Observations:

Reported data
*Statistically significant

Author's Conclusions:

Quotations of the author's primary conclusions

Review – Assessment: [NB: In actual reviews ! is replaced by: (+) denoting compliance with guidelines, (-) denoting a diversion from guidelines or (+/-) denoting a characteristic which is neither positive nor negative but is worthy of mention.]

A. Test animals:	✎ Is the number of animals sufficient to produce statistically significant results? ☐ *Guideline: 5 animals/sex/dose level; if interim sacrifices are planned numbers should be increased.* ✎ Are animal characteristics adequately recorded and appropriate for the objective of the study? a) Specie

	☐ *Guideline: Rat, or justification for use of another mammalian specie.* b) Age ☐ *Guideline: Adult, i.e.,8-12 weeks.* c) Sex d) Pre-test health ☐ *Guideline: Females should be nulliparous and non-pregnant.* e) Weight variation ☐ *Guideline: Below 20% variation* f) Source ☐ *Guideline: An established breeding facility or educational institution*
B. Exposure conditions:	✍ Was a full description (manufacturer, purity, lot no.) of the reagents used in the trial provided? ✍ Was there a gradient of exposure levels? ☐ *Guideline: Three exposure levels in addition to control.* ✍ Were the chosen exposure levels appropriate to investigate the primary objective? ✍ Were previous preliminary trials conducted to identify the range of appropriate exposure levels? ✍ Were both nominal and actual exposure concentrations recorded? ✍ Was the duration of exposure appropriate to investigate the primary objective? ✍ Was the duration of exposure precisely defined? ✍ If exposure chambers were employed, were animals exposed during the equilibration period? ☐ *Guideline: Animals should be placed in exposure chamber 4 hours after the chamber equilibrates.* ✍ Was the mode of administration appropriate? ✍ Was the frequency of administration appropriate to investigate the primary objective? ✍ Was evidence provided to justify the dosing regime? ✍ Were exposure concentrations, airflow, temperature, and humidity monitored continuously?
C. Housing/Feeding:	✍ Was the temperature, humidity, photoperiod, airflow and oxygen content maintained in the test and housing chambers

	appropriate? ☐ *Guideline: 22C (+/-3); 30-70%; 12h light/ 12h dark; 12 to 15 changes/h; 19%* ✎ Was the number of animals grouped in a single chamber stated? ☐ *Guideline: Groupings should permit clear observation of each animal.* ✎ Was the manner by which animals were grouped appropriate? ☐ *Guideline: Animals may be grouped by sex, or individually.* ✎ Was the type and source of feed and water stated? Was it appropriate? ☐ *Guideline: Conventional lab diet* ✎ Was the amount and feeding schedule specified? ☐ *Guideline: During housing, ad libitum with unlimited water; During exposure, food should be withheld and water may be withheld optionally.*
D. Equipment:	✎ Was information pertaining to the type, dimensions, material and atmospheric pressure of the exposure device outlined. ☐ *Guideline: Recommend oro-nasal or head exposure; slight negative pressure (< 5mm of water)* ✎ Was a full description of the monitoring devices provided? ✎ What was the sensitivity of the monitoring devices employed?
E. Procedural:	✎ Was the acclimation period specified? Was it of acceptable duration? ☐ *Guideline: 5 days* ✎ Was a description of the pre-test conditions (*i.e.,* diet, quarantine, disease treatment, etc.) provided? ✎ Were test animals randomly assigned to exposure groups? ✎ Was the method of randomization defined? (*i.e.,* information pertaining to the mechanism used to generate random assignment) ✎ Was a control group assayed? ✎ Is the control regime appropriate? ✎ Was the period of observation following exposure appropriate? ☐ *Guideline: Longer than 14 days.*
F. Data collection:	✎ Were appropriate endpoints examined? ✎ Was the assessment thorough (*i.e.,* information pertaining to the clinical nature, duration, reversibility, severity, onset and

	dose-response relationship was provided for each symptom)? ✍ Were accepted assessment methods employed? ✍ Were assessment measures sufficiently sensitive? ✍ Was the nature and severity of symptoms graded against an explicitly defined scale? ✍ Did qualified personnel conduct the exams? ✍ Was the timing and frequency of assessment logical? ✍ Was raw data provided to permit the reader to arrive at his/her own conclusions? ✍ Was individual data reported for each test animal?
G. Data analysis:	✍ Are the statistical methods used appropriate? ✍ Are confidence intervals reported? ✍ Did the investigator appropriately interpret the statistics? ✍ Are the observed trends statistically significant?
H. Interpretations:	✍ Was the original objective addressed? ✍ Are the results novel? ✍ Was the design of the study appropriate to investigate the primary objective? ✍ Were assumptions reasonable? ✍ Are the methods reproducible? ✍ Did either the study design or the statistical analysis limit confounding variables? ✍ Do the conclusions make biological sense? ✍ Are the extrapolations reasonable? ✍ Is the paper in a peer-reviewed journal? ✍ Would either the affiliation of the investigative team or sponsor potentially bias the conclusions reached in the document?

Review - Summary:

Discussion of findings: Reviewer's summary of study findings and interpretation of the toxicological significance and clinical relevance of these findings. Confidence index: Reviewer's assessment of the quality of the study design, conduct and reporting.

Review – Confidence index ranking:

High
High to moderate
Moderate to high
Moderate
Moderate to low
Low to moderate
Low

EPIDEMIOLOGY REVIEW FORM

Author:	**Internal ID:** ID of study within database
Title:	
Year:	
Abstract:	
Objective: The authors' stated objective and identification of relevant experiments in documents reporting findings from multiple studies.	

Overall study design:

Exposure level	Exposure frequency/duration	Gender	Age	Number of subjects	Pre-trial health	NOAEL	LOAEL

Observations:

Reported data

*Statistically significant

Author's Conclusions:

Quotations of the author's primary conclusions

Review – Assessment: [NB: In actual reviews ! is replaced by: (+) denoting compliance with guidelines, (-) denoting a diversion from guidelines or (+/-) denoting a characteristic which is neither positive nor negative but is worthy of mention.]

A. Subjects:	✍ Is the number of subjects sufficient to produce statistically significant results? ✍ Are characteristics (*e.g.,* age, sex, health, work history, medical history) of test subjects adequately recorded and appropriate for the objective of the study? ✍ Are the subjects a representative sample of the population to which extrapolations will be made? ✍ Were identical 'criteria for exclusion' applied to both cases and controls? ✍ Was the method of recruitment appropriate? Would the participation incentive employed cause the selection of an unrepresentative sample population?
B. Exposure conditions:	✍ Was the exposure concentration measured? ✍ Is the exposure duration known?
C. Equipment:	✍ Was a full description of the monitoring devices provided? ✍ What was the sensitivity of the monitoring devices employed?
D. Procedural:	✍ Was a precise definition of what constitutes 'exposure' outlined before commencement of the data retrieval? ✍ Were appropriate controls recruited? ✍ Was the type of blinding indicated? (*i.e.,* single, double, triple, etc) ✍ Was the timing and length of follow-up appropriate? ✍ Was the nature of follow-up appropriate? (*i.e.,* questionnaire, interview, medical exam, etc)
E. Data collection:	✍ Was the assessment identical for cases and controls? ✍ Were appropriate endpoints examined? ✍ Was the assessment thorough? (*i.e.,* information pertaining to the clinical nature, duration, reversibility, severity, onset and dose-response relationship provided for each symptom) ✍ Were accepted assessment methods employed? ✍ Were assessment measures sufficiently sensitive? ✍ Was the nature and severity of symptoms graded against an explicitly defined scale? ✍ Did qualified personnel conduct the exams? ✍ Was the timing and frequency of assessment logical? ✍ Was raw data provided to permit the reader to arrive at his her own conclusions? ✍ Was individual data reported for each subject? ✍ Are all withdrawals listed, with the reason for withdrawal?
F. Data analysis:	✍ Are the statistical methods used appropriate?

	✎ Are confidence intervals reported? ✎ Did the investigator appropriately interpret the statistics? ✎ Are the observed trends statistically significant?
G. Interpretations:	✎ Was the original objective addressed? ✎ Are the results novel? ✎ Was the design of the study appropriate to investigate the primary objective? ✎ Were assumptions reasonable? ✎ Are the methods reproducible? ✎ Did either the study design or the statistical analysis limit confounding variables (*e.g.,* additional chemical exposure, etc.)? ✎ Do the conclusions make biological sense? ✎ Are the extrapolations reasonable? ✎ Is the paper in a peer-reviewed journal? ✎ Would either the affiliation of the investigative team or sponsor potentially bias the conclusions reached in the document?

Review - Summary:

Discussion of findings:
Reviewer's summary of study findings and interpretation of the toxicological significance and clinical relevance of these findings.
Confidence index:
Reviewer's assessment of the quality of the study design, conduct and reporting.

Review – Confidence index ranking:

High
High to moderate
Moderate to high
Moderate
Moderate to low
Low to moderate
Low

APPENDIX 5

TABULAR SUMMARY OF STUDIES

Mortality

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Non-clinical					
▲172	Azoulay-Depuis et al., 1982	10 ppm	1 to 3 wk	Mice	Increased mortality rate, decreased survival time
◆174	Grose et al., 1986	0.95 ppm	2 hr	Mice	No change in mortality rates
◆224	Bitron and Ahronson, 1978	900, 1400 and 1900 ppm	10 to 640 min	Mice	% mortality rate increased with increased exposure time
●284	Hilado and Machado, 1977	3000 to 6800 ppm	5 to 30 min	Mice	LC_{50} 5 min 6800 ppm 10 min 4400 ppm 15 min 4000 ppm 30 min 3000 ppm
●198	Asmundsson et al., 1973	400 ppm 40-400 ppm (gradual inc.)	5 hr/d, d 5/wk, 6 wk	Rats Rats and hamsters	3 of 30 died in 1st 5 hr; 22 of remaining 27 died in 1st wk No increased mortality with gradually increasing concentrations
●218	Cohen et al., 1973	224 to 500,000 ppm	Until death or up to 4 hr	Rat	Decreased survival time with increased concentration above 590 ppm
▲183	Fedde and Kuhlmann, 1978	1000 ppm 5000 ppm	60 min	Chickens	2 of 10 birds died 9 of 10 birds died
Epidemiology *– All-cause or total mortality*					
◆336	Katsouyanni et al., 1997	38ppb increase		General population	3% increase daily mortality Western European cities 1% increase daily mortality in central eastern European cities
◆338	Xu et al., 1994	doubling of SO_2 concentrations mean: 38 ppb	One year	General population	11% increase all-cause mortality Beijing, China

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
		max: 240ppb			
◆345	Sunyer et al., 1996	38ppb increase	1985- 1991	General population	Statistically associated with total, elder & cardio mortality for whole year; same plus respiratory mortality for summer
◆349	Touloumi et al., 1996	38ppb increase	1987-1991	General population	12% increase in daily mortality risks
◆351	Dab et al., 1996	Mean daily 1 hr max = 23 ppb 24 hr = 41 ppb		General population	Significant associations with daily counts of death
◆352	Zmirou et al., 1996	19ppb increase	1985 - 1990	General population	Significant association with total mortality minus external causes, respiratory and cardiovascular deaths
◆361	Touloumi et al., 1994	10% reduction in SO_2	1984 - 1988	General population	0.65% decrease in daily mortality
◆403	Wietlisbach et al., 1996	3 day moving average	1984-1989	General population	Significant associations with total mortality minus external causes, respiratory deaths and cardio deaths
◆464	Wong et al., 2001	Average 6.5 ppb (cool season) and 6.9 ppb (warm season)		General population	Significant associations with mortality in the cool season, but not the warm season
●012	Buechley et al., 1973	190ppb	Daily average	General population	2% excess mortality when SO_2 conc. greater than 190 ppb
●334	Moolgavkar et al., 1995	100 ppb increase	1973 – 1988 Daily	General population	Significantly associated with daily mortality in the spring and winter, but not fall and summer

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
337	Spix et al., 1993	Increase from 9 ppb to 355 ppb	1980 - 1989	General population	10% excess mortality
348	Spix and Wichmann, 1996	Mean 8 and 47 ppb	Daily	General population	Increase in daily mortality of 3% for lag day
357	Glasser and Greenburg, 1971	Increase in ambient SO_2 0.20 ppm or less and days with 0.4 ppm or more	1960-64	General population	Increases in mortality, independent of weather factors in New York City
359	Krzyzanowski and Wojtyniak, 1991	Daily max 229 ppb	Winter months 1977- 1989	General population	Significance is not established for association between air pollution and daily mortality in Cracow, Poland
366	Schimmel and Greenburg, 1972	Air pollution	1963 -1968	General population	20% of excess deaths in New York City
391	Rahlenbeck and Kahl, 1996	38ppb	1981-1989 winters	General population	4.5% excess mortality in East Berlin
395	Burnett et al., 1998	0.7 – 10.5 ppb	Daily	General Population	1.4% average increased risk of mortality over 11 Canadian cites from changes in mean SO_2 concentrations
407	Le Tertre et al., 2002	19ppb increase	1990-1995	General population	Significant associations between SO_2 increase and total, cardiovascular and respiratory mortality in 9 French cities
408	Ha et al., 2003	7.8 ppb increase		General population	Some positive associations with mortality for some age groups
414	Botter et al., 2002	4 ppb increase	1991-1993	People over 65 years old	Significant 2.4% increase in daily death count for people over 65 in Sao Paulo, Brazil for a 3 day lag

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●419	Schwartz et al., 2001	4ppb increase		General population	Weak association between increase and daily deaths (0.27%, 95% CI; 0.18-0.73%) in eight Spanish cities
●434	Vedal et al., 2003	0.3-15 ppb	summer	General population	Small but significant increase in percentage total deaths was observed with a standard deviation increase in summer in Vancouver, B.C. Similar observations were made in the winter for lag 1.
●465	Odriozola et al., 1998	38ppb increase		General population	Significant associations between increase in SO_2 concentration and daily mortality
Epidemiology *– Respiratory Mortality*					
◆027	Vigotti et al., 1996	1 to 316 ppb	Daily changes over 10 y	General population	Risk of respiratory death increased with increased SO_2 concentration (RR: 1.12, 95%CI 1.03, 1.23)
◆430	Zeghoun et al., 2001	IQR increase 7-14 ppb – Rouen, France IQR increase 4-13 ppb Le Havre, France		General population	Associations with respiratory mortality in Rouen
●002	Derriennic et al., 1989	19 to 25 ppb	Daily averages	General population	Statistically significant association between daily SO_2 conc. and respiratory deaths
●412	Hong et al., 1999b	Above 40 ppb	Jan 1995 – Aug 1996	General population	Significant predictor of respiratory mortality with lag day 1, but not with total or cardiovascular mortality in Inchon, Korea
●422	Wong et al., 2002	4 ppb increase		General	Barely significant associations in

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
				population	respiratory mortalities
●440	Bobak and Leon, 1992	Range <5 - >22 ppb		Infant	Statistically significant association post neonatal respiratory mortality weak, non-significant associations for other infant mortalities
●461	Venners et al., 2003	38 ppb	One year	General population	Statistically significant associations between respiratory and cardiovascular mortality in Chongqing, China -strongest on second and third lag days
Epidemiology *– Stroke Mortality*					
●397	Hong et al., 2002b	17.43 ppb	Jan 1991 – Dec 1997	General population	Significant increased risk of ischemic stroke mortality. Hemorrhagic stroke mortality not significant.
●415	Hong et al., 2002a	5.7 ppb increase	2 day lag	General population	2.9% (95% CI: 0.8%-%.0%) increase in stroke in Seoul, Korea
◆337	Verhoeff et al., 1996	38 ppb increase	1986 - 1192	General population	No association found between air pollution and daily mortality in Amsterdam regardless of lag day
◆458	Simpson et al., 1997	60 ppb	Maximum hourly	General population	No significant association in daily mortality in Amsterdam
●332	Mazumdar et al., 1982	0.38 ppm increase	1958-1972 winters - daily	General population	No significant associations observed between daily deaths/concentrations of smoke and SO_2 in London, England
●350	Wojtyniak and Pickarski, 1996	Range of medians 11 to 28 ppb		General population	Inconsistent associations between SO_2 concentrations and cardiovascular mortalities in four Polish cities
●354	Bacharova et al., 1996	Mean: 5 to 16 ppb	1987-1991 Daily	General population	No significant association between $S0_s$ concentrations and daily number of deaths

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
		Mean: 4 – 187 ppb			in Bratislava, Slovak Republic
●355	Ballester et al., 1996	4 ppb increase	1991 – 1993 Daily	General population	No significant results reported
●400	Ballester et al., 2002	4 ppb increase		General population (13 Spanish cities)	Single city analysis – no statistically significant associations between SO_2 and daily mortality. Cities combined – associated with a 0.5% increase in daily deaths
●356	Mackenbach, 1993	Range: 5-9 ppb		General population	Positive regression coefficient for the effect of SO_2 on mortality dwindles to zero when all potential confounding factors are taken into account
●365	Anderson et al., 1996	7-17 ppb	1987-1992 warm season	General population (London)	Significant association between increased ambient SO_2 concentrations and all-cause mortality
●389	Kelsall et al., 1997	12.9 ppb increase		General population	Non-significant associations in SO_2 concentrations and total mortality.
●442	Saldiva et al., 1994	Mean: 6 ± 4 ppb	May 1990 – Apr 1991	Children (Sao, Paulo, Brazil)	No association between SO_2 concentrations and respiratory mortality
●443	Kinney and Ozkaynak, 1991	Mean 15 ± 6 ppb	`970 – 1979	General population	No association between changes in SO_2 concentration and mortality in Los Angeles County, California
●479	Kotesovec et al., 2000	38 ppb increase	Daily	General population (Northern Bohemia)	No association between daily total mortality when gender, ad, and cause of death were not separated out.

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●480	Hong et al., 1999a	4 ppb increase	Daily	General population (Inchon, Korea)	Not significant for either total or cardiovascular mortality
●483	Schwartz and Dockery, 1992	38 ppb increase		General Population (Philadelphia)	Signification positive association between total mortality and SO_2 for both current day and prior day SO_2 measurements. Total mortality estimated to increase by 5% with each 38 ppb increase in So_2.
Epidemiology *– Case Studies*					
●021	Harkonen et al., 1983	"High"	~ 20 to 25 min	Healthy adults	Death in 2 of 9 men
●270	Charan et al., 1979	"High"	Unknown	Workers	2 of 5 men died; accidental mine explosion

Respiratory System-Functional

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Clinical - Adolescents					
◆038	Koenig et al., 1982a	1 ppm	30 min rest; 10 min exercise	Adolescents with hyperactive airways	Reduction in FEV_1, V_{max50}, $V_{max\ 75}$
◆042	Koenig et al., 1982b	1 ppm	30 min rest; 10 min exercise	Healthy, adolescents	Slight reduction in FEV_1, V_{max50}, $V_{max\ 75}$ after exercise
◆099	Koenig et al., 1985	0.5 ppm	50 min	Asthmatic, adolescents	Reduction in FEV_1, V_{max50}, $V_{max\ 75}$
◆103	Koenig et al., 1987	0.75 ppm	10 min	Asthmatic, adolescents	Decreased FEV_1; increased total respiratory resistance
◆102	Koenig et al., 1990a	1 ppm	10 min	Asthmatic, adolescents	Decreased FEV_1; increased total respiratory resistance

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
◆277	Koenig et al., 1990b	100 ppb	15 min	Asthmatic, adolescents	Slight decrease in FEV_1 and V_{max50}
Clinical *- Effects observed-healthy subjects*					
▲060	Stacy et al., 1981	0.75 ppm	2 hours	Healthy adults	Increased SRaw
▲096	Kulle et al., 1986	1 ppm	4 hr/d; 3d/wk, 3wk	Healthy adults	Decreased spirometric function
◆045	Newhouse et al., 1978	5 ppm	2.5 hr	Healthy adults	Decreased MMFR, increased bronchial clearance
◆047	Bedi et al., 1984	1 to 2 ppm	2 hours	Healthy adults	Increased SRaw
◆056	Wolff et al., 1975	5 ppm	3 hr	Healthy adults	Decreased MMF
◆070	Snell and Luchsinger, 1969	0.5, 1, 5 ppm	15 min	Healthy adults	Decreased $MEF_{50\%VC}$ at 1 and 5 ppm
◆072	Kagawa, 1983	0.15 ppm	2 hr	Healthy adults	Decreased specific airway conductance; increased residual capacity and residual volume
◆063	Andersen et al., 1974	1, 5, 25 ppm	6 hr/d; 3 d	Healthy adults	Decreased nasal mucus flow rate; increased nasal airflow resistance
◆318	Islam, et al., 1994	0.73 ± 0.05 00m	5 minutes	Healthy non-smoking adults	Statistically greater increase in SRaw after hyperventilation with SO_2
◆048	Andersen et al., 1977	5 ppm	4 hr	Healthy adults	Decreased nasal mucus flow rate in anterior nose
●069	Nadel et al., 1965	4 to 6 ppm	10 min	Healthy adults	Decreased airway conductance and thoracic gas volume
●076	Frank et al., 1964	1-2, 4-6, 14-17 ppm	30 min	Healthy adults	Increased pulmonary flow resistance at 4-6 and 14-17 ppm
●323	Frank et al., 1961	1,5,15 ppm		Healthy male adults	Most results were not significant and there was substantial variability among the volunteers

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●121	Douglas and Coe, 1987	1 ppm	Eyes: 15 s Lungs: 10 breaths	Healthy adults	Threshold for bronchoconstriction
●032	Amdur et al., 1953	1 to 8 ppm	10 min	Healthy adults	Decreased tidal volume; increased respiratory rate
●317	Lawther et al., 1975	1 to 30 ppm	10 min to one hour	Healthy adults	Normal breathing at 1ppm – no significant changes Deep breathing at 3 ppm – no significant changes Hyperventilation of 1 ppm (undetermined period of time) – small but significant changes in SRaw Quiet breathing of 10,15,20 and 30 ppm for 10 min at each concentration – significant changes for most
●324	Sim and Pattle, 1957	Maximum 2160 mg min/m^3 (mask) and 3620 mg min/m^3 (chamber)		Healthy male adults	800 mg min/m^3 – no effects Above 1300 mg min/m^3 – resistance to air flow significantly increased in half the volunteers exposed by mask and chamber. At this dosage and higher, high pitched musical rales observed
●416	Whittenberger and Frank, 1963	1, 5 and 13 ppm	Unidentified	Work colleagues	Increased specific airway resistance
Clinical - No effects observed: healthy subjects					
▲043	Stacy et al., 1981	0.75 ppm	4 hr	Healthy adults	No effect
◆039	Kreisman et al., 1976	0.5 to 5 ppm	1 to 5 min	Healthy adults	No effect

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
◆051	Bedi et al., 1979	0.4 ppm	2 hr	Healthy adults	No effect
◆049	Bedi et al., 1982	0.4 ppm	2 hr	Healthy adults	No effect
◆122	Folinsbee et al., 1985	1 ppm	2 hr	Healthy adults	No effect
◆040	Kulle et al., 1984	1 ppm	4 hr/day, 3 d/wk, 3 wk	Healthy adults	No effect
●087	Sandstrom et al., 1988	0.4 to 4 ppm	20 min	Healthy adults	No effect
●325	Lawther, 1955	0, 5,10,20 ppm	10 min each by nose and mouth	Healthy male adults	No effect
Clinical - No effect healthy subjects: effects asthmatics					
▲073	Jaeger et al., 1979	0.5 ppm	3 hr	Normal, asthmatic	Normal: no effect Asthmatic: decreased MMF
◆306	Schachter et al., 1984	0,0.25,0.50, 0.75 and 1.0 ppm	40 min	Normal, asthmatic	Healthy subjects – no pulmonary function changes at all concentrations or in asthmatics below 1.0 ppm At 1.0 ppm significant changes in SRaw and FEV_1 at max flow at 50% of vital capacity
◆309	Linn et al., 1987	0,0.2,0.4 and 0.6 ppm	1 hr including three 10 min exercise periods	Normal, atopic, asthmatic	Normal and Atopic – little response at all levels Moderate to severe asthmatics - increasing response with increased dose
●092	Tan et al., 1982	2.5 to 20 ppm	5 min	Normal, asthmatic	Normal: no effect Asthmatic: decreased specific airway conductance

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●108	Harries et al., 1981	Up to 15 ppm	Not clear	Normal, asthmatic	Normal: no effect; Asthmatic: decreased FEV_1 at 5 to 11.5 ppm
Clinical – Effects observed – asthmatic subjects					
▲077	Gong et al., 1995	0.5, 1 ppm	10 min	Asthmatic adults	Dose-dependent changes in pulmonary function parameters
▲081	Roger et al., 1985	0.25, 0.5, 1 ppm	75 min	Asthmatic adults	Increased SRaw at 0.5 and 1 ppm
▲109	Jorres and Magnussen, 1990	0.5, 0.75 ppm	30 min	Asthmatic adults	Change in SRaw
◆055	Trenga et al., 1999	0.5 ppm	10 min	Asthmatic adults	Decreased FEV_1
◆064	Balmes et al., 1987	0.5 or 1 ppm	1, 3, 5 min	Asthmatic adults	Small increases in SRaw; wheezing, tightness of chest, dyspnea
◆071	Tunnicliffe et al., 2001	200 ppb	1 hr	Asthmatic adults	Increased respiratory frequency
◆375	Sheppard et al., 1980	1,3, 5ppm	10 min	Asthmatic adults	Increased SRaw occurred at lower concentrations (1 ppm) in mild asthmatics At 5 ppm all asthmatics exhibited significant increases in SRaw
◆062	Tam et al., 1988	2 ppm 4 ppm	4 min 10 min	Asthmatic adults	Increased dyspnea, wheezing, SRaw
◆078	Kehrl et al., 1987	1 ppm	1 hr	Asthmatic adults	Increased SRaw
◆098	McManus et al., 1989	0.5 or 1 ppm	30 min	Asthmatic adults	Dose-dependent effect on FEV_1, total airway resistance, V_{max50}, V_{max75}
◆110	Heath et al., 1994	1 ppm	20 min	Asthmatic adults	Decreased V_{max50}, R_T, FEV_1
◆118	Bethel et al., 1985	0.25 ppm	10 min	Asthmatic adults	Increased SRaw
◆303	Horstman et al., 1986	0.25,0.5,1.0,2.0 ppm	10 min	Asthmatic adults	Substantial variability observed in bronchial sensitivity SRaw 100% greater than the response

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
					to clean air ranged between 1.28 and 1.90 ppm for 23 subjects – for remaining subjects greater than 2.0 ppm
◆304	Linn et al., 1983 a	0.75 ppm	10 min (chamber) -once with encumbered breathing, once with nose clips	Asthmatic adults	Greater increase in SRaw observed upon exposure to SO_2 than clean air exposure Excess increase significantly greater with mouthpiece than with unencumbered breathing
◆310	Linn et al., 1983 b	0,0.2,0.4 and 0.6 ppm	5 min	Asthmatic adults	Dose-response effect with only the changes at 0.6 ppm being highly significant
◆311	Horstman et al., 1988	1.0 ppm		Asthmatic adult	During mild exercise, significant increases in bronchoconstriction occurred at 2.0 minutes of exposure
◆326	Bethel et al., 1983	0.5 ppm	5 min	Asthmatic adults	Bronchoconstriction observed during moderate to a greater degree with heavy exercise when breathing through mouthpiece and during heavy exercise when breathing through a facemask.
◆376	Sheppard et al., 1981b	010,02.5,0.50 and 1 ppm (mouthpiece)	5-10 min	Mild Asthmatics	Significant bronchoconstriction observed for most at 0.25 ppm
●084	Wolff et al., 1984	5 ppm	2.5 hr	Asthmatic adults	Increased bronchial reactivity
●116	Fine et al., 1987	8 ppm	Up to 1 min	Asthmatic adults	Increased SRaw

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●316	Linn et al., 1984 c	0.6 ppm for 6 hour periods on two successive days	1 hr	Asthmatic adults	Volunteers exercised heavily for 5 min at beginning of exposures and after 5 hours of exposure. Substantial bronchoconstrictive response were observed only immediately after exercise
Clinical *- No effects observed: asthmatic subjects*					
▲075	Bailey et al., 1982	0.25, 0.5 ppm	1 hr	Asthmatic adults	No effect
◆067	Devalia et al., 1994	200 ppb	6 hr	Asthmatic adults	No effect
◆101	Linn et al., 1985b	Up to 0.8 ppm	1 hr	Asthmatic adults	No effect
Clinical *- Effect and recovery*					
◆061	Sheppard et al., 1983	0.5 ppm	3 min, 3 x 30 min intervals	Asthmatic adults	Increase SRaw in first exposure; less increase in second & third exposures
◆079	Hackney et al., 1984	0.75 ppm	3 hr	Asthmatic adults	Increased SRaw initially; decreased to pre-exposure levels after 1 hr of exposure
◆097	Linn et al., 1998	0.3, 0.6 ppm	10 min	Asthmatic adults	Increased bronchoconstriction; returned to normal by 30 min post-exposure
◆260	Gokemeijer et al., 1973	10 ppm	3 min	Asthmatic adults	Bronchial obstruction; returned to control by 45-60 min post-exposure
●053	Toyama and Nakamura, 1964	1 to 60 ppm	5 min	Healthy adults	Increased SRaw returning to control values post-exposure
Clinical *- Nose vs. mouth exposure*					
◆054	Speizer and Frank, 1966b	15 or 28 ppm	10 min	Healthy adults	Increased pulmonary flow resistance; more from oral than nasal exposure
◆074	Kirkpatrick et al., 1982	0.5 ppm	5 min	Asthmatic adults	Increased SRaw; greater with oral than nasal exposure

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
◆105	Melville, 1970	2.5 to 10 ppm	10 min to 1 hr	Healthy adults	Decreased specific airway conductance; greater effect with oral than nasal exposure
◆266	Bedi and Horvath, 1989	2 ppm	30 min	Healthy adults	Difference in ventilatory parameters between forced oral and free-breathing exposures
Clinical *- Temperature and humidity*					
◆057	Sheppard et al., 1984	0.1 ppm	3 min	Healthy adults	Bronchoconstriction at lower concentrations in dry air than humidified air
◆123	Bethel et al., 1984	0.5 ppm	3 min	Healthy and asthmatic adults	Increased SRaw with SO_2 in cold dry air with asthmatics
◆314	Linn et al., 1984 a	0, 0.3 and 0.6 ppm Temperatures 21°C, 7°C and -6°C - constant humidity of 80%	5 min	Asthmatic adults	Considerable variability – cold seemed to exacerbate the overall response to SO_2
●313	Linn et al., 1984 b	0, 0.2,0.4 nd 0.4 ppm 85% (high) and 50% (low) relative humidity	5 min heavy exercise	Asthmatic adults	Bronchoconstriction increased with increasing SO_2 concentrations, but did not vary significantly with humidity
◆307	Linn et al., 1985a	0.6 ppm 21°C and 38°C humidity 20%	5 min heavy exercise	Asthmatic adults	Greater effects on SRaw observed at low temperature and low humidity

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Non clinical - Effects observed-bronchial clearance					
◆235	Ferin and Leach, 1973	0.1 ppm 1 ppm	70 hr 170 hr	Rats	Slight decrease in lung clearance
◆256	Mannix et al., 1983	20 ppm	4 hr	Rats	Delayed early clearance of upper respiratory tract
◆213	Oomichi and Kita, 1974	15, 32, 58, 77 ppm	2 to 6 min	Guinea pigs	Dose-dependent decrease in ciliary activity
●132	Riechelmann et al., 1995	3, 6, 9, 11, 14 ppm	30 min	Guinea pigs	Dose-dependent decrease in mucociliary activity
●164	Knorst et al., 1994	2.5, 5, 7.5, 10, 12.5 ppm	30 min	Guinea pigs	Decrease in mucociliary activity at 2.5 ppm; Dose-dependent decrease in ciliary beat frequency above 5 ppm
●134	Trimpe et al., 1986	27±3 ppm	35 d	Hamsters	Decrease in lung clearance
●129	Wakabayashi et al., 1977	1.4 to 66 ppm	16hr/d, 7 d	Chickens	Increased intranasal transport time
●137	Ukai et al., 1984	18 to 40 ppm	1 hr/d, 7 d	Chickens	Decrease in turbinate clearance
●138	Ukai et al., 1983	4 to 40 ppm	1 hr, 4x/d for 2d	Chickens	Increases in nasal turbinate clearance time
●149	Majima et al., 1985	6 ppm	16 hr/d, 7 d	Chickens	Decrease in mucociliary transport rate
Non-clinical *- Effects observed-bronchoconstriction/specific airway resistance*					
▲183	Fedde and Kuhlman, 1978	100 ppm 500 ppm 1000 ppm	60 min	Chickens	Increase in minute volume Decreased SRaw Initial decrease then increase in SRaw; increased respiratory frequency, decreased minute volume
▲197	Barthelmy et al., 1988	0.5 or 5 ppm	45 min	Rabbits	Dose-dependent increases in lung resistance
◆244	Davenport et al.,	200 to 400 ppm	15 to 20 min	Rabbits	Decreased breathing frequency;

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
	1984				increased tidal volume
●194	Citterio et al., 1985b	300 to 350 ppm	Unreported	Rabbits	Increased inspiratory and expiratory time
●234	Davies et al., 1978a	200 ppm	10 min	Rabbits	Increased inspiratory time; decreased expiratory time
▲259	Park et al., 2001	0.1 ppm	5 hr/d, 5 d	Guinea pigs	Increased respiratory pause
◆189	Atzori et al., 1992	50 to 500 ppm	15 min	Guinea pigs	Reduced dynamic compliance
◆229	Amdur et al., 1983	1 ppm	1hr	Guinea pigs	Increased respiratory resistance; decreased compliance
◆245	Halinen et al., 2000a	1, 2.5, 5	10 min each, consecutive	Guinea pigs	Dose-dependent increase in bronchoconstriction at 1 and 2.5 ppm
◆246	Halinen et al., 2000b	1 ppm	1 hr	Guinea pigs	Weaker effects than previous study
●216	Amdur, 1959	2 to 1000 ppm 24 ppm	1 hr 3 hr	Guinea pigs	Increased bronchial constriction
●227	Amdur and Underhill, 1970	1.5 to 26 ppm	1 or 2 hr	Guinea pigs	Increased airway resistance
◆243	Alarie et al., 1973	17, 32, 62, 89, 123, 198, 298 ppm	10 min	Mice	Dose-dependent respiratory depression
◆253	Leong and MacFarland, 1965	40, 64, 83, 145, 231, 426, 751 ppm	2 hr	Rats	Dose-dependent decrease in % SO_2 retention, respiratory rate, minute volume; increase in tidal volume
●167	Cho et al., 1968	11 to 1000 ppm	0.1 to 6 min	Dogs	Bronchoconstriction at all levels
●170	Frank et al., 1965	7 to 230 ppm	15 to 20 min	Dogs	Increased nasal and pulmonary flow resistance
●258	Lewis and	10 and 30 ppm	5 min	Dogs	Increased lung hypersensitivity to

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
	Kirchner, 1984				aerosolized methacholine
●190	Eady and Jackson, 1989	400 ppm	2 hours	Dogs	Increase in bronchial response to histamine
●162	Islam et al., 1972	1, 2, 5, 10 ppm	3x60-min periods	Dogs	Increased bronchial sensitivity
●146	Norris and Jackson, 1989	200 ppm	2 hr	Dogs	Increased airway hyperreactivity
●170	Frank and Speizer, 1965	7-16 ppm, 25-34 ppm or 60-61 ppm	20 min	Dogs	Increased nasal and pulmonary flow resistance
●186	Grunstein et al., 1977	3000 to 7000 ppm	24 to 40 seconds	Cats	Reduced tidal volume, increased respiratory frequency and pulmonary resistance
●290	Corn et al., 1972	15-25 or 30-40 ppm	30 min	Cats	Pulmonary flow resistance – lower then 20 ppm no response; at 20ppm only one animal showed a response
●372	Thompson et al., 1990	100,500,800 and 1000 ppm	1,5,10 breaths	Cats	Concentration dependent response was observed in lung resistance with the administration of 10 breaths of 100 – 1000 ppm
◆230	Abraham et al., 1981	5 ppm	4 hr	Sheep, normal and allergic	Increased airway reactivity in asthmatic sheep 24 hr after exposure
◆231	Abraham et al., 1980	5 and 10 ppm	4 hr	Sheep, normal and allergic	Increased airway reactivity in both sheep 24 hr after exposure to 10 ppm
●205	Spiegelman et al., 1968	27 to 713 ppm	30 min	Miniature donkeys	No effects
◆191	Giddens and Fairchild, 1972	10 ppm	4 to 72 hr	Mice	Lesions of olfactory and respiratory epithelium

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
◆207	Ukai, 1977	0.03 to 0.1 ppm	4 wk	Mice	More rapid and more severe inflammatory response to influenza infection
◆238	Fairchild, 1977	6 ppm	7 d	Mice	Inhibition of virus growth
●300	Hanacek, 1987	200-300 ppm	10-15 min	Rabbits	Decrease in mechanically stimulated cough excitability and cough reflex strength
Non Clinical *- No effects observed*					
◆204	Amdur et al., 1978	0.2, 0.4, 0.8 ppm	2 hr	Guinea pigs	No effects
◆257	McJilton et al., 1976	1 ppm	2x60 min	Guinea pigs	No effects
●226	Amdur and Underhill, 1968	2 ppm	10 min	Guinea pigs	No effects
●263	Lippman et al., 1975	35 to 300 ppm	30 min	Donkeys	No effects
●161	Hanacek et al., 1991	200 to 300 ppm	10 to 20 min	Rabbits	No effects
Epidemiology - Children					
◆005	Boezen et al., 1999	Approx. 0.22 to 23 ppb (ambient)	Unknown	Asthmatic children	Children with bronchial hyperresponsiveness and high serum IgE concentrations are more susceptible to increases in air pollution
◆013	Dockery et al., 1982	64 to 174 ppb (ambient)	SO_2 spikes over 2-year period	Children	Slight decrease in pulmonary function with increasing SO_2 conc.
◆018	Hoek and Brunekreef, 1993	Ambient, range unknown	SO_2 spikes over three	Children	Decreased FVC, FEV1, MMFR with SO_2 concentrations > 38 ppb

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
			winters		
◆426	Schwartz et al., 1994	Ambient, range unknown	Unknown	Children	Not significantly associated with cough incidence or upper respiratory symptoms Lower respiratory symptoms above concentrations of 22 ppb
◆448	Segala et al., 1998	Ranged from 1.7 to 32 ppb Mean: 8.3 $\pm$ 5.1 ppb	Same Day Lag day 1	Asthmatics (Paris)	Significant increase in incidence of asthma attack in mild asthmatics with an increase of 19 ppb
◆449	Roemer et al., 1993	40 ppb and 56 ppb	24 hr average and 1 hr max	Children (The Netherlands)	Small but statistically significant negative association between SO_2 concentrations for both morning and evening peak flow
●362	Agocs et al., 1997	Unknown	Unknown	Asthmatic children (Budapest, Hungary)	Longitudinal study of lung peak expiratory flow rates and ambient air pollution – no consistent, significant association
●385	Romieu et al., 1995	Unknown	Unknown	Children (Mexico City)	Statistically significant associations between total number of emergency visits for respiratory disease and levels of SO_2 on the same day Associations between number of emergency visits for asthma or total number of emergency visits and SO_2 concentration were not statistically significant.
●394	Lin et al., 2003	Unknown	Lagged over	Children	Significant association between

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
			6 or 7 days	(Toronto, Ontario)	asthma hospitalization and exposure to SO_2 in girls aged six to twelve, but not in boys
●398	Lee et al., 2002	4.4 ppb increase (ambient)	Unknown	Children (South Korea)	Statistically significant association between hospital admission for asthma
●413	Delfino et al., 2003	Increases in ambient		Hispanic children (Los Angeles)	Significant associations between bothersome and more severe asthma symptoms with increases in ambient SO_2
●456	Chew et al., 1999	7.6 ppb increase	Lagged by 1 or 2 days	Children (Singapore)	Significant positive correlation between 7.6 ppb increase in SO_2 levels lagged by 1 or days and daily asthma emergency room visits
●469	Hajat et al., 1999	6.8 ppb change in ambient levels		General population	Statistically significant association between GP consultations for asthma and other lower respiratory diseases in children. No significant findings reported for adults and the elderly.
●432	Mortimer et al., 2001		2 day moving average lag increase	Asthmatic children (4-9) (USA)	Association between a 2-day moving average lab increase in SO_2 and morning asthma symptoms
●485	Garty et al., 1998			Asthmatic children	Positive correlations between emergency room visits for acute asthma attacks and ambient mean SO_2 concentrations.

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●435	Peters et al., 1996	51 ppb increase		Children (East Germany and Czech Republic)	Weak association between 51 ppb SO_2 increases and decreases peak expiratory flow
●445	Queiros et al., 1990		Monthly Quarterly	Children (Oporto area of Portugal)	Very small significant correlations between monthly and quarterly mean ambient SO_2 concentrations and asthmatic attacks
●450	Braun-Fahrlander et al., 1992	Range 11-27 (ambient)	Unknown	Children (two cities in Switzerland)	No statistically significant associations between ambient levels and respiratory symptoms
●451	Henry et al., 1991	Ambient	Unknown	Children (Two towns, New South Wales, Australia)	No significant association between ambient SO_2 levels and asthma symptoms
●457	Kieding et al., 1995	Unknown	Unknown	Children	No association between SO_2 levels and number of total contacts or contacts for respiratory illness with the Copenhagen Emergency Medical Service in children.
●462	Yu et al., 2000	Unknown	Unknown	Children (Seattle., Washington)	No significant association between ambient SO_2 concentrations and asthma symptoms
●467	Roemer et al., 1998	Unknown	Morning Evening	Asthmatic children	No clear association between SO_2 and morning or evening PEF
Epidemiology *– Hospital admissions or other incidence of chronic obstructive pulmonary disease (COPD)*					
◆351	Dab et al., 1996	Mean 11 ppb Mean 23ppb	24 hour 1 hr max	General population (Paris)	Significantly associated with admission for COPD for same-day exposure
◆369	Anderson et al.,	19 ppb increase		General population	Varied considerably across the cities

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
	1997	in daily mean		(Europe)	(Amsterdam, Barcelona, Paris, Rotterdam); not statistically significant for all ages In the warm season, borderline significant results between hospital admissions for COPD and a 19 ppb increase in daily means SO_2 levels with inconsistent lags of either the same day or day 2
◆406 ◆402	Desqueyroux et al., 2002a,b	0.76 to 10 ppb (mean: 2.7 ± 1.9 ppb) 1.1 to 31 ppb (mean: 7.3±4.6 ppb)	Summer Winter		No association between physician-monitored exacerbation of COPD symptoms or asthma
◆431	Tenias et al., 2002	4ppb increase		General population (Valencia, Spain)	Not associated with emergency room visits for COPD
●439	Sunyer et al., 1991	38ppb (daily mean)		General population (Barcelona)	Small but statistically significant association between daily number of emergency room admissions and daily levels of SO_2 Increase of 38 ppb daily means led to an average of 2 additional admissions per day
●437	Sunyer et al., 1993	9.5 ppb increase (ambient)	5 year period winter and summer	General population (Barcelona)	Resulted in 6% increase in emergency admissions in winter and 9% in summer

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●481	Wong et al., 1999	4ppb increase (ambient)		General population	Weak and barely significant associations between increase of 4 ppb in ambient SO_2 levels and hospital admissions for respiratory disease and COPD
Epidemiology *– Hospital admission or clinic visits for respiratory disease and/or asthma*					
◆367	Bates and Sizto, 1987	2.21 to 5.14 ppb (winter) 1.65 to 3.97 (summer)	Jan, Feb, Jul and Aug 1974 and 1976-1983	General population (southern Ontario)	Significant correlations were found between SO_2 and deviations form the mean respiratory admissions for day of the week, season and year.
◆340	Walters et al., 1994	15ppb and 48 ppb		General population (Birmingham, UK)	Daily SO_2 levels were weakly, but significantly associated with hospital admissions for respiratory diseases for the same day in the summer and with a two-day lag in the winter.
◆423	Wong et al., 2002	4 ppb increase		General population (Hong Kong and London, England)	Asthma admissions were not significantly associated with in either city. Respiratory admissions was small, but significant in Hog Kong
●342	Emerson, 1973	Atmospheric conditions and air pollution	82 weeks, weekly	32 Volunteers	SO_2 was reported to be significantly correlated with FEV_1 in one volunteer and with MEFR in two volunteers
●346	Ponce de Leon et al., 1996		1987-1992	General Population (London)	Weak and questionably significant associations were reported between an increase in SO_2 concentrations from the 10^{th} to the 90^{th} percentile

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
					and two different age groups and two seasons.
●347	Ponka and Virtanen, 1996b	Mean 5-10 ppb	24 hour	General population	Positive associations – asthma admissions
●393	Hwang and Chan, 2002	1.5 to 16.9 ppb mean: 5.4±3.0 ppb		General population (Taiwan)	Significant associations between current day SO_2 concentrations and daily number of clinic visits for lower respiratory illness People over 65 most susceptible and associations decreased as lag day increased
●399	Martins et al., 2002		Six day	General population (Sao Paulo, Brazil)	Significant association between a six-day moving average of SO_2 and emergency room visits for chronic lower respiratory disease in the elderly
●409	Jaffe et al., 2003	19 ppb increase	Daily	Asthmatics (Cincinnati, Cleveland, and Columbus, Ohio)	12% increased risk of an emergency department episode with a 19 ppb increase in SO_2 across all cities
●410	Hajat et al., 2002	5.7 and 7.8 ppb		General population (London, England)	Significant increases in the number of physician consultations for upper respiratory disease for adults and those 14 years and younger Elderly – no significant changes
●428	Pinter et al., 1996			General population	Significant correlations between daily concentrations of SO_2 and incidence of acute respiratory morbidity
●444	Hoek and	Mean		General population	Small significant positive

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
	Brunekreef, 1994	5.7±5.5ppb		(Netherlands)	associations between previous day SO_2 concentrations and daily respiratory symptoms, but no pulmonary function.
●471	Schwartz, 1995			General population (two cities, USA)	SO_2 levels were significant predictors of hospital admissions for respiratory disease with very different ratios of SO_2-to-PM. The lag day differed between two cities
●472	Peters et al., 1997	25 ppb increase (5 day mean levels of SO2)	Evening	General population (Czech Republic)	Weak, but statistically significant decrease in evening peak expiratory flow.
Epidemiology *– Other asthma incidence*					
◆333	Moseholm et al., 1993	6.5 to 6.8 ppm	24 hr means 8-month period	Asthmatics	Lung function was associated with ambient SO_2 concentrations of SO_2, as well as with temperature, relative humidity, and medicine intake Increased SO_2 concentrations corresponded to decreased peak flow levels above 15ppb
●364	Buchdahl et al., 1996		Daily		Significant associations between variations in daily SO_2 concentrations and the incidence of acute wheezy episodes, after adjustment for season
●433	Tarlo et al., 2001	Ambient	March to November		
●455	Neukirch et al.,	19 ppb increase	5 day lag	Asthmatics	Significant associations and incidence

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
	1998		(winter)	(Paris)	of wheeze and nocturnal cough SO_2 levels correlated significantly with decreased morning peak expiratory flow
Epidemiology *– Other hospital admissions*					
●453	Ponka, 1991		Daily		Significant correlations of daily concentrations of SO_2 and admissions to emergency wards in the elderly
Epidemiology *– No associations observed*					
◆023	Kesten et al., 1995	0 and 0.15 ppm	Year Long	General population	No association was observed between SO_2 and emergency room visits Some association with other air pollutants
●331	Moolgavkar et al., 1997	Unknown	1986-1991	General population (Minneapolis St. Paul, Minnesota and Birmingham, Alabama)	No significant associations between hospital admissions and SO_2 concentrations
●353	Schouten et al., 1996	11ppb – Amsterdam 15 ppb – Rotterdam	24 hour mean	General population (Amsterdam and Rotterdam)	Results inconsistent with both negative and positive associations observed between SO_2 concentrations and hospital admissions for respiratory disease.
●425	Tenias et al., 1998	10 ppb	24 hour mean	General population (Valencia, Spain)	No significant associations between SO_2 levels and emergency room visits for asthma in an ecological study as part of the APHEA project
●454	Burnett et al., 1999		Daily	General population	No statistically significant associations between daily hospital

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
					admissions for respiratory and daily measures of SO_2
●470	Harre et al., 1997	(ambient)	Morning Evening peak	General population (Christchurch, New Zealand)	No significant association between ambient SO_2 levels in either morning or evening peak expiratory flow rate.
●473	Prescott et al., 1998	10 ppb increase (moving average)	3 days	General population (Edinburgh)	No statistically significant change in the risk of hospital admissions
●475	Hernandez-Garduno et al., 1997	Unknown	Unknown	Patients (clinics, Mexico City)	Ambient So_2 levels negatively correlated with patient visits to clinics in Mexico City
●478	Holmen et al., 1996	Measurements 10 m off the ground	Daily		No statistically significant correlations between emergency department visits for asthma and daily ambient SO_2 levels.
●482	Sheppard et al., 1999	10 ppb increase (ambient)		General population (Seattle)	No significant associations between a 10ppb increase in ambient SO_2 levels and hospital admissions for asthma
●484	Castellague et al., 1995			General population (Barcelona Spain)	No statistically significant associations between ambient SO_2 levels and emergency room visits
Epidemiology *- Workers*					
◆007	Donoghue and Thomas, 1999	Up to 3300 ppb (ambient)	Unknown	Asthmatics	No relationship between peak ambient SO_2 and hospital presentations or admissions for asthma
◆009	Zuskin et al., 2000	Up to 190 ppb (ambient)	Unknown	Outdoor workers *vs.* indoor controls	Increased prevalence of upper airway symptoms in outdoor workers

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
◆016	Holness et al., 1985	Average: 0.47 ppm	Occupational exposure	Nickel smelter workers	Higher prevalence of cough, dyspnea, decreased FVC, FEV_1 over workweek
●017	Likas et al., 2001	0.15 to 0.66 ppm	Occupational exposure	Greenhouse workers	No effects on lung function
●029 ●030 ●031	Lawther et al., 1974 a, b, c)	FEV_1 MMF Peak expiratory flow	Every working for five years	Four normal subjects (central London)	MMF showed most consistent association with pollution levels Respiratory infections had a substantial effect on pulmonary measurements Outdoor exercise had some association with decreases in FEV_1 and MMF None of the associations reported to be significant
Epidemiology – *Case reports*					
●021	Harkonen et al., 1983	Unknown (Accidental exposure)	Approx. 20 to 25 min	Healthy adults	Death in 2 of 9 men; in survivors: thoracic pain, coughing, decreased FVC, FEV_1, MMFR, bronchial hyperreactivity
◆001	Piirila et al., 1996	Unknown (Accidental exposure)	Approx. 20 to 25 min	13-year follow-up of Harkonen et al., 1983	Bronchial hypersensitivity in all patients; obstructive ventilatory impairment
◆272	Rabinovitch et al., 1989	Unknown (Accidental exposure)	Unknown	2 miners	Severe airway obstruction, hypoxemia, active inflammation three weeks after accident
●269	Woodford et al., 1979	Unknown (Accidental	Unknown	Previously healthy young male	Rhinorrhea, cough, pulmonary edema, pulmonary obstructive

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
		exposure)			syndrome
●271	Galea, 1964	Unknown (Accidental exposure)	Unknown	35-year old male	Cough, dyspnea, wheezing, death 17 days after exposure

Respiratory System-Biochemical

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Clinical					
◆033	Speizer and Frank, 1966a	Approx. 16 ppm	Unreported	Adults	SO_2 absorbed in the upper respiratory tract
◆052	Field et al., 1996	0.5 to 8 ppm	Unreported	Asthmatic adults	SO_2 responsiveness decreased with opioid and increased with cyclooxygenase inhibitor
◆066	Bechtold et al., 1993	1 or 7 ppm	10 to 20 min every other day for 3 wk	Asthmatic adults	S-sulfonate conc. In nasal lavage fluid is a potential short-term biomarker of exposure to SO_2
◆083	Sandstrom et al., 1989a	4 and 8ppm	20 min	Healthy adults	Increased alveolar activity in bronchoalveolar lavage fluid (BAL)
◆090	Sandstrom et al., 1989b	8 ppm	20 min	Healthy adults	Increases in macrophages, lymphocytes, and mast cells in BAL
●091	Sandstrom et al., 1989c	4, 5, 8, 11 ppm	20 min	Healthy adults	Dose-dependent increase in mast cells, lymphocytes, macrophages in BAL up to 8 ppm
◆085	Witek and Schachter, 1985	1 ppm	40 min	Asthmatic adults	Correlation between increased dose of SO_2 and dose of methacholine required
◆321	Lazarus et al., 1997	8.0 ppm	4 min	Asthmatic	Leukotriene receptor antagonist

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
					zafirlukast inhibited SO_2 induced bronchoconstriction in 12 subjects
Non-clinical					
◆133	Riedel et al., 1988	0.1 to 16.6 ppm	8 hr/d, 5 d	Guinea pigs	Increased antigen-specific antibodies in serum and bronchoalveolar fluid
◆163	Haider, 1985	10 ppm	1 hr/d, 30 d	Guinea pigs	Increased conc. Cholesterol, total lipids, gangliosides; decreased phospholipids
◆178	Atson et al., 1991	250 ppm	10 min	Guinea pigs	No attenuation of SO_2-induced bronchoconstriction with inhalation of two different medications
◆245	Halinen et al., 2000	1, 2.5, 5 ppm	10 min	Guinea pigs	Decreased proportion of macrophages in white cells
●370	Hajj et al., 1996	500,100,1500 and 2000 ppm		Guinea pigs	Tachykinin release from sensory endings does play a role in SO_2 induced bronchoconstriction
●452	Ito et al., 1995	800 ppm	2 hrs	Guinea pigs	Direct epithelial injury from SO_2 inhalation results in loss of epithelial cells and an increase in permeability
◆155	Kahana and Aronovitch, 1968	800 ppm 1225 ppm	1 hr 2 hr	Rats	Reduction in minimal and maximal pulmonary surface tension Pulmonary edema, greater reduction in surface tension
◆206	Vai et al., 1980	600 ppm	30 to 100 hr	Rats	Increased mucosal permeability
◆251	Langley-Evans et al., 1996	5, 50, 100 ppm	5 hr/d, 7 to 28 d	Rats	Decreased glutathione conc. And inflammation at 100 ppm
◆252	Husain and Dehnen, 1978	46.5 ppm	up to 4 wk	Rats	No change in benzo(a)pyrene metabolism

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●181	Barry and Mawdesley-Thomas, 1970	300 ppm	6 hr/d, 10 d	Rats	Increased acid phosphatase and β-glucuronidase, and β-galactosidase activity
●193	Grause and Barker, 1978	5 to 20 ppm	7 d	Rats	Dose-related increase in electrophoretic bands from nasal mucous
●262	Kahana and Aronovitch, 1966	627-751 ppm 257-450 ppm	1 hr 9 x 4 hr	Rats	Decreased surface forces and transpulmonary pressures Results unclear
◆207	Ukai, 1977	0.03 to 0.1 ppm	4 wk	Mice	Increased response to viral challenge
▲374	Skornik and Brain, 1990	50 ppm		Hamsters	Significant reduction observed after 40 minutes of continuous running while breathing 50 ppm SO_2 No changes with non-exercise, between exercise with SO_2 and no exercise without SO_2
●147	Rana et al., 1979	500 ppm	5 min	Squirrels	Changes in lung lipids and membrane permeability
●149	Majima et al., 1985	6 ppm	16 hr/d, 7 d	Chickens	Decreased nasal mucous elastic recoil distance *in vivo*
●199	Okuyama et al., 1979	3.4 to 18.5 ppm	1 to 14 d	Chickens	Increased in mononuclear and polymorphonuclear cells, and number of plasma cells
●221	Bauer, 1981	350 to 400 ppm	3 hr	Chickens	Decreased glycoprotein conc.
◆150	Man et al., 1986	100 ppm 500 ppm	75 min	Dogs	No change in bioelectric properties Changes to bioelectric properties and increased nonelectrolyte permeability

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
◆225	Azoulay et al., 1980	2 ppm	1 to 49 d	Rats	No changes observed

Respiratory Effects - Structural

Clinical					
◆320	Kienast et al., 1994a	2.5 to 12.5 ppm at 37°C and 100% humidity	30 min		Dose-dependent decrease in ciliary beat frequency observed from low to high concentrations
●427	Kienast et al., 1996	0, 2.5, 5.0, 7.5, 10.0 and 12.5 ppm	30 min	12 healthy volunteers	Dose-dependent decrease in ciliary beat frequency observed
●466	Riechelmann et al., 1994	2.5, 5, 7.5, 10, and 12. 5 ppm	30 and 120 min		Concentration-dependent reduction in ciliary beat frequency in human nasal cells
●046	Carson et al., 1985	0.75 ppm	2 hr	Normal adults	Increased prevalence of compound cilia
Non-clinical					
●132	Riechelmann et al., 1995	3, 6, 9, 14 ppm	30 min	Guinea pigs	Dose-dependent decrease in mucociliary activity, but only minor morphological changes
◆250	Knauss et al., 1976	600 and 700 ppm	3 hr/day for 9, 18, or 30 hrs	Rats	Increase in solid material recovered by bronchial lavage
◆305	Stratmann et al., 1991	800 ppm	8 hrs	Rats	Gradient of decreasing damage in the tracheobronchial tree in the peripheral direction Most severe lesions in trachea epithelium

●166	Gross et al., 1969	2500 and 4000 ppm	15 min	Rats	Edema found in the separation of the surface epithelium from the alveolar septum
●210	Pariente, 1980	600 ppm 1000 ppm	100 hr 4 hr	Rats	Acute bronchitis, bleeding of rhinopharynx, chronic tracheobronchial injuries
●447	Hong, 1996	30 to 50 ppm	4 or 12 hr	Rats	No significant changes in cell count, LDH, total protein, CC16, and lysozyme bronchoalveolar lavage fluid
●477	Farone et al., 1995	230 ppm	1 day	Rats	Substantially increased numbers of polymorphonuclear leukocytes in tracheas
◆191	Giddens and Fairchild, 1972	10 ppm	4 to 72 hr	Mice	Decrease in thickness of olfactory mucosa, severe rhinitis
●208	Weiss and Weiss, 1976	40 ppm	6 to 9 d	Mice	Increase in static lung compliance
●287	Min et al., 1994	20 ppm increased	30 to 60 to 120 min	Mice	60 – 120 minutes - Injuries included edema, loss of cilia, epithelial thinning, and epithelial desquamation 30 minutes – no changes
●198	Asmundsson et al., 1973	40, 100, 200, 250, 400 ppm	5 hr/d, 5 d/wk, 6 wk	Hamsters	Epithelial damage in large airways after one week
◆468	Blanquart et al., 1995	10 and 30 ppm	1 hr	Rabbits	Ciliary activity was significantly inhibited
●294	Dalhamn and Strandberg, 1961	200 ppm	45 min	Rabbits	Ciliary movement stopped when 10ppm SO_2 or greater was blown directly onto the trachea
●417	Strandberg, 1964	0.05 to 700 ppm		Rabbits	Differences in the absorption of high concentrations of SO_2 and low

					concentrations in the respiratory tract
●286	Frank et al., 1967	22±2 ppm	30 to 60 min	Dogs	Investigation of uptake of SO_2 into body fluids
●418	Balchum et al., 1959	1.1-141 ppm	20 to 40 minutes	Dogs	Investigation of uptake of SO_2 into body fluids
◆308	Knorst et al., 1996a	1.0,25. and 5.0 ppm	30 min	Human in vitro	Functional impairment of human alveolar macrophages after exposure
●319	Knorst et al., 1996b	0.5, 1.5 and 2.5 ppm	15 min	Human in vitro	Changes in AM and BM chemotactic activity Cell viability not affected

Respiratory System – Signs and Symptoms

Clinical *– Effects observed*					
◆039	Kreisman et al., 1976	0.5 to 5 ppm	1 to 5 min	Healthy adults	Dryness, irritation or burning of the throat
◆063	Andersen et al., 1974	1 to 25 ppm	6 hr/d, 3 d	Healthy adults	Discomfort proportional to SO_2 conc.
◆064	Balmes et al., 1987	0.5 or 1.0 ppm	1, 3, or 5 min	Asthmatic adults	Chest tightness, wheezing, dyspnea
◆093	Witek et al., 1985	less than 1 ppm	40 min	Health and asthmatic adults	Chest tightness, wheezing, dyspnea, cough
Clinical *– No effects observed*					
◆072	Kagawa, 1983	0.15	2 ppm	Healthy adults	No effects observed
Non-clinical studies					
●125	Amdur, 1954	89 ppm	8 to 16 hr	Guinea pigs	Few signs of respiratory distress
●142	Matsumura, 1970	20, 60, 180, 330 ppm	30 min	Guinea pigs	Sneezing, rubbing eyes and noses, uneasiness at 330 ppm
●144	Matsumura et al., 1972	450, 600, 700 ppm	30 min	Guinea pigs	No increased sensitivity to acetylcholine challenge
Epidemiology *– Effects observed*					

◆011	Cohen et al., 1974	0.11 to 0.15 ppm	Peak hourly conc.	Healthy adults and children	Increased reports of eye and throat irritation, chest discomfort, shortness of breath, restricted activity, medical visits
◆010	Carnow et al., 1969	up to 0.30 ppm	10 months	Adults with chronic bronchopulmonary disease	Dose-response association between SO_2 conc. greater than 0.25 ppm and percent person-days of illness
◆016	Holness et al., 1985	0.47 ppm	Average	Nickel smelter workers	Higher prevalence of cough, dyspnea, lower baseline function over the workweek
Epidemiology *– No effects observed*					
◆015	Love et al., 1982	4 to 46 ppm	Annual mean ambient conc.	Elementary school children	No effects
◆018	Hoek and Brunekreef, 1993	up to 38 ppb	Winter	Children	No effects
●004	Franklin et al., 1985	Not reported	10 d	Asthmatic and non-asthmatic children	No effects
●006	Ayres et al., 1989	Polluted area: 19-40 ppb Non-polluted area: 13-27 ppb	Unreported	General population	No effects
●267	NIOSH, 1984	Up to 1.03; 0.2 to 1.8 ppm	Unreported	Cement plant workers	Shortness of breath, frequent colds, cough, sore throat, chest tightness; association with SO_2 exposure unclear

Respiratory System - Other

◆182	Fairchild et al.,	3.4 to 34.5 ppm	7 d	Mice	Increased incidence of pneumonia

	1972				after exposure to SO_2
●126	Suzuki, 1969	10 and 50 ppm	3 hr	Guinea pigs	No effect on water or histamine content of lungs
●169	Frank et al., 1969	1 to 50 ppm	1.5 to 5 min	Dogs	Most inhaled SO_2 is absorbed in the nose

Signs and Symptoms

Clinical *– Effects observed – healthy subjects*					
▲096	Kulle et al., 1986	1 ppm	4 hr/d, 3 d/wk, 3 wk	Healthy adults	Increased nose and throat irritation
◆054	Speizer and Frank, 1966b	15 and 28 ppm	10 min	Healthy adults	Coughing, burning sensations in throat and substernal area
◆063	Andersen et al., 1974	1 to 25 ppm	6 hr/d, 3 d	Healthy adults	Some discomfort, proportional to SO_2 concentration
●053	Toyama and Nakamura, 1964	1 to 60 ppm	5 min	Healthy adults	Reported objective odours, irritation of upper respiratory tract and unusual sensations in lung
●087	Sandstrom et al., 1988	0.4 to 4 ppm	20 min	Healthy adults	Irritation of throat, unpleasant smell
Clinical *– Effects observed – asthmatic subjects*					
▲077	Gong et al., 1995	Up to 0.5 ppm	1 hr	Asthmatic adults	Decreased lung function with increased SO_2 conc.
◆064	Balmes et al., 1987	0.5 and 1 ppm	1, 3, and 5 min	Asthmatic adults	2 of 8 subjects reported chest tightness at 1 ppm for 1 min; 7 of 8 reported wheezing and chest tightness after 0.5 ppm for 3 and 5 min
◆079	Hackney et al., 1984	0.75 ppm	3 hr	Asthmatic adults	Increased asthma symptoms after 10 minutes of vigorous exercise, decreasing to normal by 1 hr post-exposure

◆041	Koenig et al., 1981	1 ppm	30 min at rest, 10 min exercise	Asthmatic children	Shortness of breath, wheezing
●087	Roger et al., 1985	1 ppm	10 min	Asthmatic young male	Shortness f breath and chest discomfort Trend towards increased wheezing, deep breathing discomfort, and cough
Clinical – *Effects observed – healthy and asthmatic subjects*					
◆093	Witek et al., 1985	< 1 ppm	40 min	Healthy and asthmatic adults	Increased chest tightness, wheezing, cough, dyspnea in asthmatics and taste and odour complaints from healthy subjects with increased SO_2 concentration
Clinical – *No effects observed*					
▲075	Bailey et al., 1982	0.25, 0.5 ppm	1 hr	Asthmatic adults	None observed
◆072	Kagawa, 1983	0.15 ppm	2 hr	Healthy adults	No symptoms observed
◆101	Linn et al., 1985b	0.4, 0.8, 1 ppm	1 hr	Chronic pulmonary obstructive disease	No observed effects
Clinical – *Eye Symptoms*					
●121	Douglas and Coe, 1987	3 to 60 ppm	Eye: 1 s Lung: 10 breaths	Healthy adults	Eye: dose-dependent, reversible response
Non-clinical					
▲159	Haider et al., 1981	10 ppm	1 hr/d, 21 d	Guinea pigs	Nasopharyngitis, somnolence, staggering, itching, preening, skin and eye irritation
◆261	Johnson et al., 1972	40 ppm	4 to 11 d	Mice	Reversible effects: depressed feed and water intake, decreased body weight and O_2 consumption
●142	Matsumura, 1970a	20, 60, 180, 300	30 min	Guinea pig	No signs of irritation lower than 300

		ppm			ppm
●143	Matsumura, 1970b	400 ppm	30 min	Guinea pig	Some signs of irritation
Epidemiology					
◆007	Donoghue and Thomas, 1999	Up to 3300 ppb	Peak concentrations over a 3 yr period	Asthmatic population	No association between peak SO_2 concentrations and hospital presentations or admissions for asthma, wheeze or shortness of breath
◆011	Cohen et al., 1974	0.01 to 0.15 ppm	2 elevated air pollution events, 1 low air pollution period	General population	Increase in reported eye and throat irritation, chest discomfort, shortness of breath, restricted activity and medical visits during high pollution events
●424 ●474	Xu et al., 1995 a, b	38 ppb increase	Daily	General population	A 38ppb increase in SO_2 associated with internal medicine and pediatric outpatient visits, and emergency room visits.
●429	Park et al., 2002	2.68 to 28.11 ppb	Unknown	Elementary school children	Associated with illness-related absences from school
Epidemiology – *Case reports*					
◆272	Rabinovitch et al., 1989	"High"	Brief, accidental	Workers	Airway effects, reduced exercise tolerance
●021	Harkonen et al., 1983	"High"	Brief, accidental	Workers	Thoracic pain, coughing, conjunctival irritation, corneal erosion
●271	Galea, 1964	"High"	Brief, accidental	Workers	Dry irritable cough, dyspnea, copious amounts of mucous 10 d post-exposure
●269	Woodford et al., 1979	"High"	Brief, accidental	Workers	Burning and tearing eyes, rhinorrhea, cough, almost passing out
●270	Charan et al., 1979	"High"	Brief,	Workers	Irritation and soreness of eyes, nose

			accidental		and throat, tightness in chest, intense dyspnea, severe conjunctivitis and corneal burns

Cardiovascular System

Clinical					
◆071	Tunnicliffe et al. 2001	200 ppb	1 hr	Healthy and asthmatic	Differences in "total power" in healthy subjects
●032	Amdur et al., 1953	1 to 8 ppm	10 min	Healthy	No effect
Non-Clinical					
▲183	Fedde and Kuhlman, 1979	100 ppm 5000 ppm	1 hr	Chickens	No effect @ 100 ppm Increased heart rate @ 5000 ppm
◆211	Wang et al., 1996	5000 ppm	2 breaths	Rats	Decreased heart rate; no change in blood pressure (BP)
◆233	Callanan et al., 1974	100 to 400 ppb	1 to 3 min	Geese	Increased BP and heart rate
●241	Drew et al., 1983	50 ppm	6 hr/d, 5 d/wk, 6 wk	Rats	Decreased blood pressure in hypertension-resistant rats; increased BP in other rats
◆251	Langley-Evans et al., 1996	5 to 100 ppm	5 hr/d, 7-28 days	Rats	Decreased glutathione in the heart
◆163	Haider, 1985	10 ppm	1 hr/d, 30 days	Guinea pigs	Increased cholesterol, total lipids, phospholipids and decreased gangliosides in the heart
●147	Rana et al., 1979	500 ppm	4 min	Squirrels	Decreased lipid levels and increased moisture content in heart
●237	Balchum et al., 1960	1.8 to 148 ppm	30 to 40 min	Dogs	Low, uniform $^{35}SO_2$ concentration in heart muscle
Epidemiology					

◆423	Wong et al., 2002	4 ppb increase		General Population (Hong Kong and London, England)	Significant positive association between 4 ppb increase and daily admissions for cardiac diseases
●459	Sunyer et al., 2002	Range 1.9 – 8 ppb	Same-day	General population	Significant increase in daily numbers of all cardiovascular admissions except stroke and particularly ischemic heart disease
●387	Morris et al., 1995	0.05 ppm	Unknown	General Population (US cities)	Inconsistent results for association between an increase of 0.5 ppm SO_2 and hospital admissions for congestive heart failure Highest average SO_2 levels – New York Lowest average SO_2 levels – Los Angeles
Cardiovascular – Epidemiology- *No association observed*					
●002	Derriennic et al., 1989	19 to 25 ppb	Unreported	General population	No statistically significant correlation
●388	Ponka and Virtanen, 1996a	0.08 – 36 ppb range	Unknown	General population	No significant associations with hospital admissions for ischemic cardiac and cerebrovascular diseases.
●441	Peters et al., 2000	Mean 0.007 ppm	Unknown	(Massachusetts)	No association between implanted cardioverter defibrillator discharges and SO_2 concentrations

Eye

Clinical					
▲096	Kulle et al., 1986	1 ppm	4 hr/d, 3 d/wk, 3 wk	Healthy adults	No adverse effects
●065	Coe and Douglas,	50 ppm	5 min	Healthy adults	No subjective effect reported

	1982				
●121	Douglas and Coe, 1987	3 to 60 ppm	15 s	Not reported	Threshold for tear production = 5 ppm
Non-Clinical					
▲159	Haider et al., 1981	10 ppm	1 hr/d, 21 d	Guinea pigs	Signs of eye irritation
Epidemiology					
◆011	Cohen et al., 1974	0.01 to 0.15 ppm	Unreported	General population	Eye irritation reported during both high and low pollution periods
●267	NIOSH, 1984	0.2 to 1.8 ppm	5 to 8 months	Workers	Eye irritation present; link to SO_2 exposure undetermined
●021	Harkonen et al., 1983	"high levels"	20-45 min	Workers	Conjunctival irritation, corneal erosion
●269	Woodford et al., 1979	"high concentrations"	15-20 min	Workers	Burning and tearing of eyes

Gastrointestinal System

Non-Clinical					
◆460	Meng et al., 2003	8.4±0.8, 21±1, 43±3 ppm	Unreported	Mice	Increased levels of lipid peroxidation in stomachs and intestines of male and female mice

General Biochemical Effects

Clinical					
◆055	Trenga et al., 1999	0.5 ppm	10 min	Asthmatic adults	No correlation between plasma antioxidant concentrations and sensitivity to SO_2
◆312	Kienast et al., 1994b	0.3 to 1.5 ppm	30 and 60 min	Unknown	No conclusive evidence as to the measured amount of ROI that is sufficient to induce clinically relevant pulmonary fibrosis
●112	Gunnison and	0.3, 1, 3, 6 ppm	up to 120 hr	Health smokers and non-	Positive correlation between plasma

	Palmes, 1974			smokers	S-sulfonate and atmospheric SO_2
●265	Grote and Thews, 1973	Unreported	Unreported	Adults, health status not reported	Amount of SO_2 dissolving in human blood increases with increasing blood O_2 and CO_2 and decreasing blood pH
Non-clinical					
◆236	Etlik et al., 1995	10 ppm	1 hr/d, 30 d	Guinea pigs	Increased methemoglobin, sulfhemoglobin, lipoperoxidation, osmotic fragility
●142	Matsumura, 1970	330 ppm	30 min	Guinea pigs	Hematoglutination in 5 of 10 exposed animals
●254	Lee and Danner, 1966	6-310 ppm	60 min	Guinea pigs	Increased hemoglobin @ all concs.; Increased inorganic sulphur in blood above 19 ppm
▲152	Lovati et al., 1996	5 and 10 ppm	15 days, continuous	Rats	Dose-dependent increase in plasma triglycerides and increase in HDL cholesterol (normal and hypertensive rats); decrease in plasma triglycerides and increase in HDL cholesterol (diabetic rats)
◆151	Jonek et al., 1976	Unreported	50 min	Rats	Highest concentration in blood 2 hr post-exposure
◆192	Baskurt, 1988	0.87 ppm	24 hr	Rats	Whole blood and packed cell viscosities decreased
◆225	Azoulay et al., 1980	2 ppm	1 to 49 d	Rats	No effects observed
●193	Gause and Barker, 1978	5 to 20 ppm	7 d	Rats	10% of inhaled SO_2 found in blood or plasma within 1st 30 min of exposure
●302	Baskurt et al., 1990	1 ppm		Rats	No significant effects on hemoglobin
◆212	Vanjonack and Johnson, 1972	40 ppm	0.5 to 24 hr	Mice	Decreased plasma thyroxine levels at 12 and 24 hr exposure; increased plasma glucocorticoids at 1 and 12 hr

●380	Meng et al., 2002	5 to 32 ppm		Mice	Increased frequencies of polychromatic erythrocyte micronuclei formation (MNPCE)
●222	Gunnison and Benton, 1971	23.5 ppm	14 to 62 hr	Rabbits	Increased plasma and serum S-sulfonate levels
▲183	Fedde and Kuhlman, 1978	up to 5000 ppm	60 min	Chickens	No change at 100 ppm; Decreased blood pH and O_2, increased blood CO_2 at 5000 ppm

Immunological System

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Clinical					
◆035	Winterton et al., 2001	0.5 ppm	10 min	Asthmatic adults	Increased response to SO_2 is associated with the wild-type allele of THF-alpha promoter polymorphism
◆048	Anderson et al., 1977	5 ppm	4 hr	Healthy adults	50% decrease in nasal mucous flow; no difference in # of people developing colds
◆083	Sandstrom et al., 1989a	4, 8 ppm	20 min	Healthy adults	Dose-dependent increase in macrophage activity 24 post-exposure
●091	Sandstrom et al., 1989c	4, 5, 8, 11 ppm	20 min	Healthy adults	Increased macrophage activity 24 post-exposure; return to pre-exposure levels within 72 hr post-exposure
◆103	Koenig et al., 1987	0.75 ppm	10 min	Allergic adults, no asthma	Investigation of mechanism of action of SO_2-induced bronchoconstriction
●058	Sheppard et al., 1981a	0.5 or 1 ppm	10 min	Asthmatic adults	Investigation of mechanism of action of SO_2-induced bronchoconstriction
Non-clinical					
▲172	Azoulay-Depuis et	10 ppm	up to 3 wk	Mice	Increased mortality, decreased

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
	al., 1982				survival time in exposed, infected mice
◆207	Ukai, 1977	0.03 to 0.1 ppm	4 wk	Mice	Antibodies to virus developed more rapidly and increased # of goblet cells
◆238	Fairchild, 1977	6 ppm	7 d	Mice	Inhibition of influenza virus growth
●134	Trimpe et al., 1986	27 ppm	Not clear	Hamsters	No difference in bacterial clearance rates
▲259	Park et al., 2001	0.1 ppm	5 hr/d, 5 d	Guinea pigs	Enhanced ovalbumin-induced asthmatic reactions
◆133	Riedel et al., 1988	0.1 to 16.6 ppm	8 hr/d, 5 d	Guinea pigs	Increased ovalbumin-specific antibodies and bronchoalveolar fluid
●201	Gause and Rowlands, 1975	Unclear	Not reported	Human lymphocyte membranes	Dose-dependent spectral change
◆209	Watson and Brain, 1980	250 ppm	3 hr	Mice	Increased uptake of Fe in airway epithelium
●199	Okuyama et al., 1979	3.4 to 18.5 ppm	1 to 14 d	Chickens	Increased # of macrophages, lymphocytes, plasma cells and neutrophils
●146	Norris and Jackson, 1989	200 ppm	2 hr	Dogs	Increased airway permeability to plasma proteins and cell shedding
Epidemiology					
◆005	Boezen et al., 1999	0.3 to 22 ppm	3 months/yr, 3 yr	Adolescents	Children with bronchial hypersensitivity and high serum IgE levels were more susceptible to air pollution (not SO_2 specifically).

Kidney and Liver

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Non-clinical					
▲152	Lovati et al., 1996	5 and 10 ppm	15 days	Rats	Increased liver triglycerides in normal rats; decreased liver weight and liver triglycerides in diabetic rats
◆163	Haider, 1985	10 ppm	1 hr/d, 30 d	Guinea pigs	Decreased phospholipids, cholesterol, and lipid peroxidation in liver and kidney
◆251	Langley-Evans et al., 1996	5 to 100 ppm	5 hr/d, 7-28 d	Rats	Decreased glutathione levels in liver and kidney; decreased glutathione reductase activity
●237	Balchum et al., 1960	1.8 to 148 ppm	30 to 40 min	Dogs	Second highest SO_2 conc. found in kidney; low conc. in liver.

Metabolic System

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Non-clinical					
◆261	Johnson et al., 1972	40 ppm	4 to 11 d	Mice	Decreased metabolism as measured by O_2 consumption
◆381	Meng, 2003	20 ppm	6 hr /day for 7 days	Mice	Decreased activist of Se-dependent glutathione peroxidase in all organs of both sexes Significant decrease of catalase activity in livers from both sexes
◆251	Langley-Evans et al., 1996	5-100 ppm	5 hr/d, 7-28 d	Rats	Varied enzyme activity in lung, liver, heart, kidney

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
●273	Leung et al., 1985	Not reported	Single dose	Rats	Metabolite of SO_2 inhibits glutathione s-transferase in liver and lungs
***Non-clinical** – Lipid metabolism*					
▲152	Lovati et al., 1996	5 or 10 ppm	15 d	Rats	Dose-dependent increase in plasma triglycerides, decreased HDL cholesterol in normal rats; decreased plasma and liver triglycerides, increased HDL cholesterol in diabetic rats
◆163	Haider, 1985	10 ppm	1 hr/d, 30 d	Guinea pigs	Changes in lipid metabolism varying by organ; decreased lipid peroxidation

Nervous System

Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Non-clinical, Behavioural					
▲214	Petruzzi et al., 1996	5, 12, 30 ppm	24 d	Mice	Changed behaviour after exposure
◆217	Fiore et al., 1998	5, 12, 30 ppm	14 d	Mice	Changed behaviour in adults after prenatal exposure
Non-clinical, Biochemical					
▲159	Haider et al., 1981	10 ppm	1 hr/d, 21 d	Guinea pigs	Decreased total lipids and free fatty acids; lipid content and enzyme activity vary depending on brain area
◆249	Haider et al., 1982	10 ppm	1 hr/d, 30 d	Rats	Lipid content and enzyme activity vary depending on brain area
Non-clinical, Functional					
▲197	Barthelmy et al., 1988	0.5, 5 ppm	45 min	Rabbits	

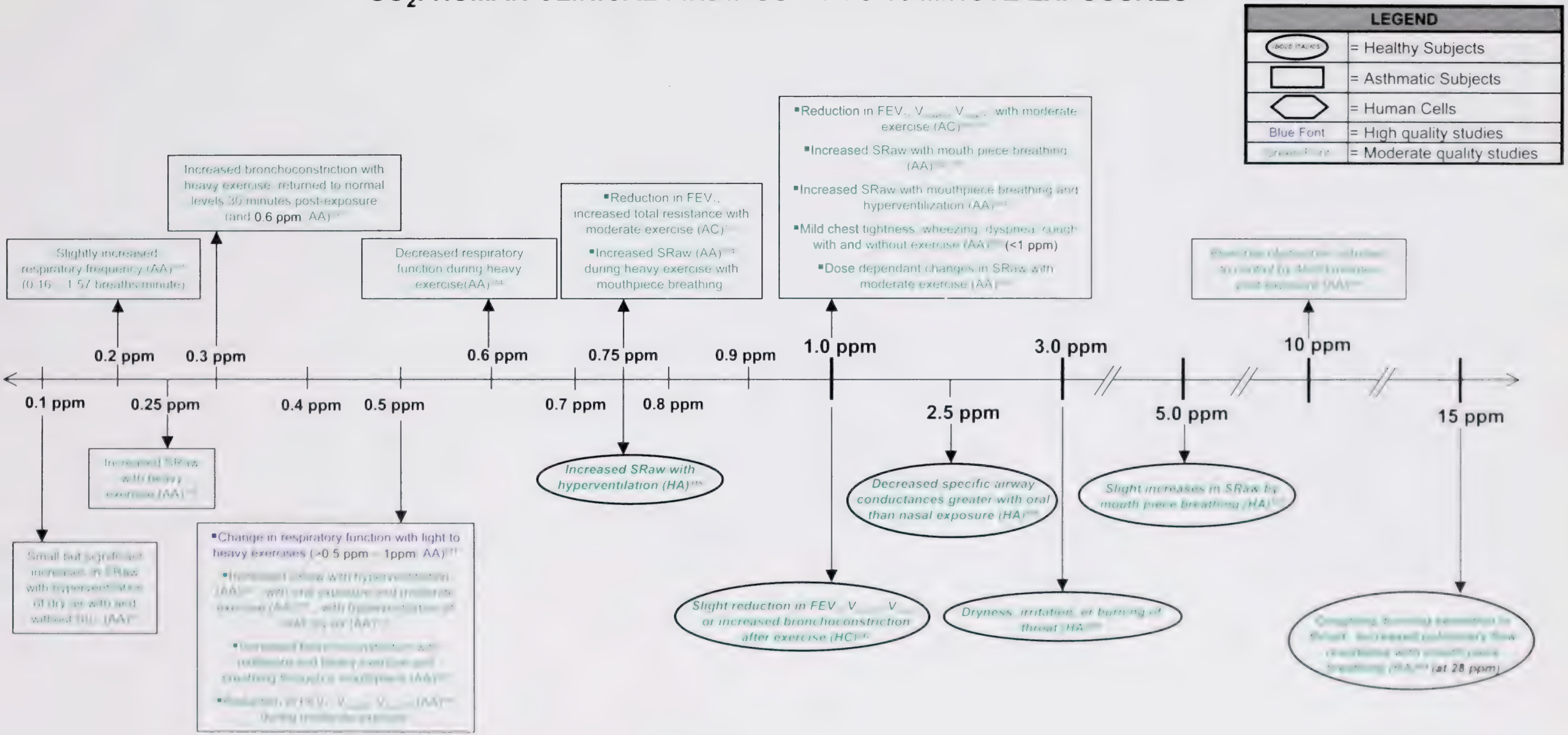
◆153	Karpas and Widdicombe, 1983	20000 ppm	single dose	Ferrets	Investigation of the reflexive nature of SO_2-induced bronchoconstriction
◆200	Matsumoto et al., 1997	200 ppm	Unknown	Rabbits	
◆211	Wang et al., 2001	5000 ppm	2 breaths	Rats	
●237	Balchum et al., 1960	1.8-148 ppm	30-40 min	Dogs	
◆239	Davies et al., 1978b	150 ppm 300 ppm	12x 3 hr 3 hr	Rabbits	
◆244	Davenport et al., 1984	200-400 ppm	15-20 min	Rabbits	
●069	Nadel et al., 1965	Unknown	Unknown	Cats	
●141	Mortola et al., 1985	300-350 ppm	10-15 min	Rabbits	
●161	Hanacek et al., 1991	200-300 ppm	10-20 min	Rabbits	
●167	Cho et al., 1968	100-10000 ppm	0.1-6 min	Dogs	
●194	Citterio et al., 1985a	300-350 ppm	Unknown	Rabbits	
●195	Citterio et al., 1985b	300-350 ppm	15-20 min	Rabbits	
●234	Davies et al., 1978a	200 ppm	1-5x 10 min	Rabbits	

Reproductive System

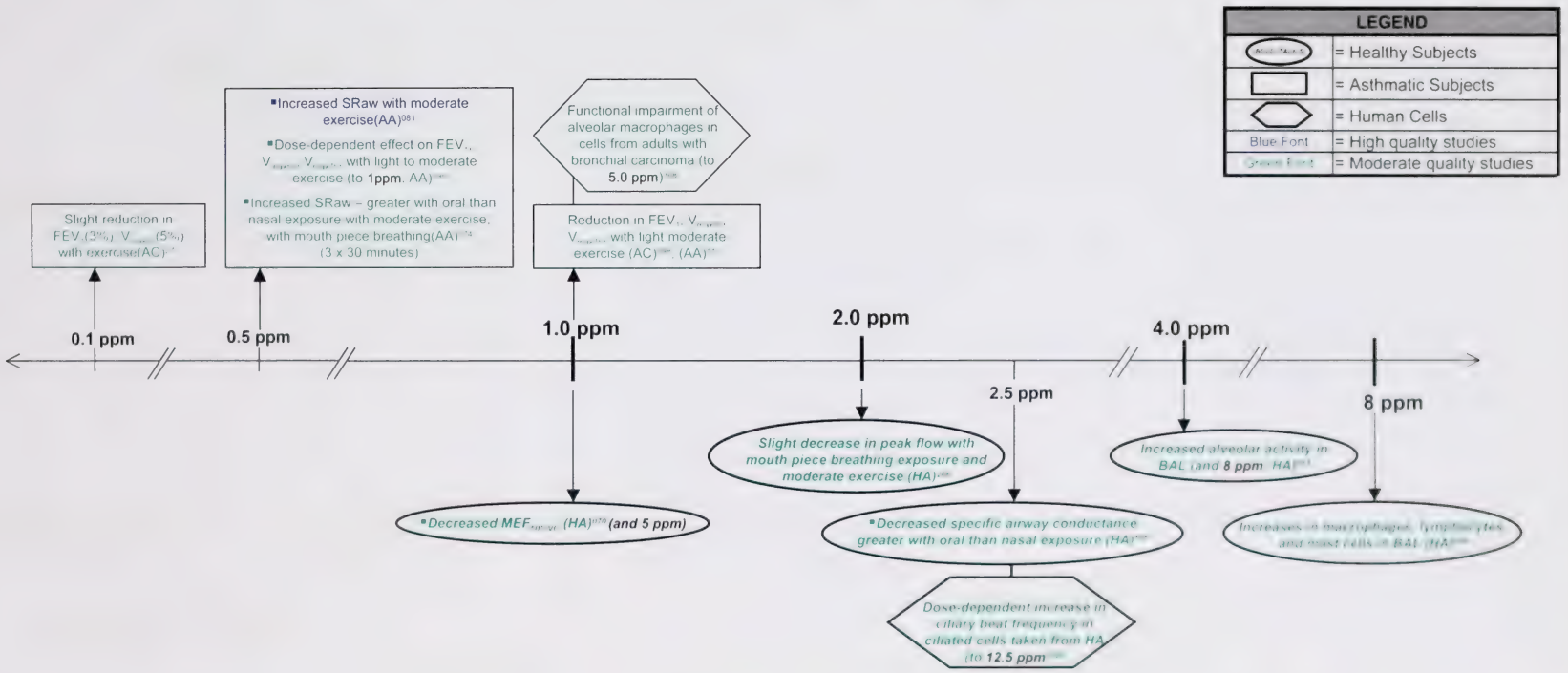
Study ID	Reference	SO_2 Concentration	Time	Species/Population Group	Effect
Non-clinical					
◆203	Singh, 1982	32, 65, 125, 250 ppm	Gestational days 7 to 17	Mice	No effect on # of dead or reabsorbed fetuses; no teratological effects; decreased pup weight at 65 and 125 ppm
◆140	Murray et al., 1979	25 ppm 70 ppm	Gestational days 6 to 15 Gestational days 6 to 18	Mice Rabbits	Decreased mean fetal body weight; delayed ossification of sternebrae and occipital bone Minor skeletal variations
▲214	Petruzzi et al., 1996	5, 12, 30 ppm	From 9 days pre-pregnancy to gestational	Mice	No changes observed in reproductive performance of neurobehavioural development of offspring

			day 12-14		
◆217	Fiore et al., 1998	5, 12, 30 ppm	Gestational days 1 to 14	Mice	Enhancement in body sniffing and self-grooming behaviour; increased other social behaviour; decreased tail rattling, freezing and defensive behaviours
Epidemiology					
●003	Dolk et al., 2000	Unreported; based on distance from point source	Unreported	General population	No evidence of adverse birth outcomes with respect to distance from cokeworks (point source of SO_2)

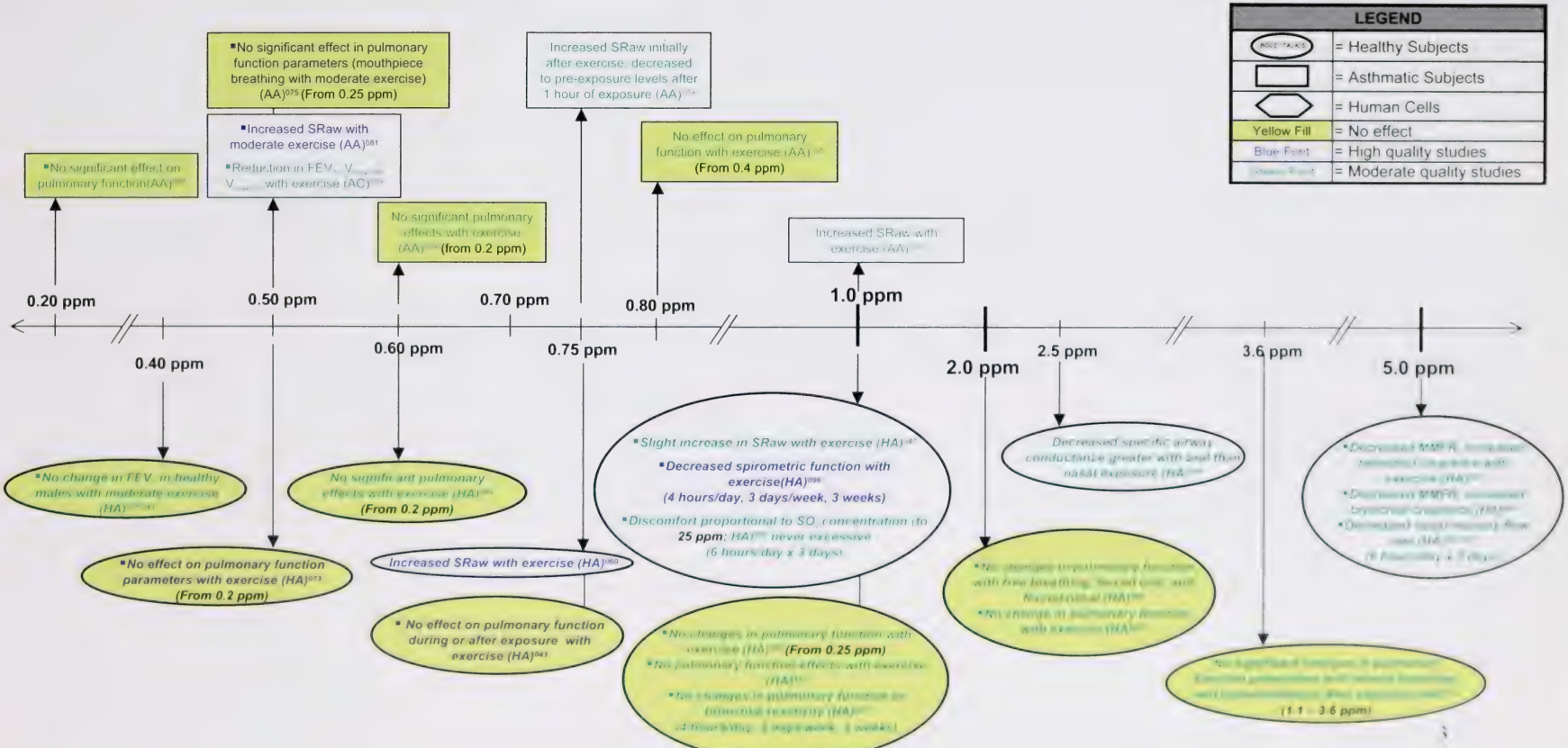
RESPIRATORY EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO SO_2: HUMAN CLINICAL FINDINGS – *1 TO 10 MINUTE EXPOSURES*



RESPIRATORY EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO SO_2: HUMAN CLINICAL FINDINGS – *11 TO 30 MINUTE EXPOSURES*

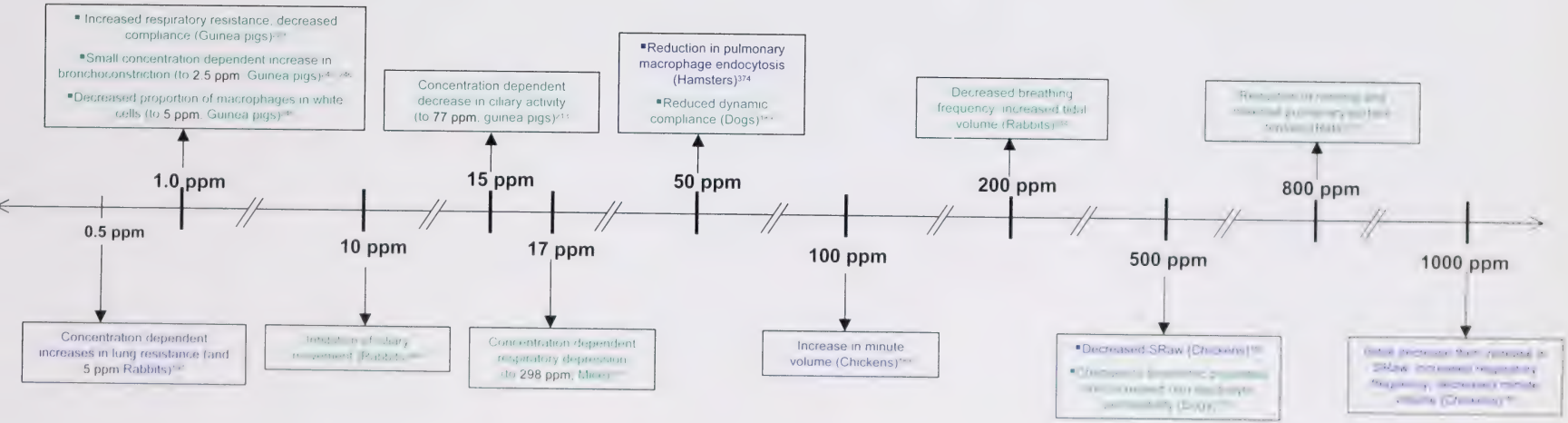


RESPIRATORY EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO SO_2: HUMAN CLINICAL FINDINGS – *30 MINUTE TO 4 HOUR EXPOSURE AND 3 DAYS TO 3 WEEK EXPOSURE*



RESPIRATORY EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO SO_2: ANIMAL TOXICOLOGY STUDIES – *UP TO 2 HOUR EXPOSURES*

LEGEND	
Blue Font	= High quality studies
Green Font	= Moderate quality studies



RESPIRATORY EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO SO_2: ANIMAL TOXICOLOGY STUDIES – *2 HOUR TO 1 DAY EXPOSURES*

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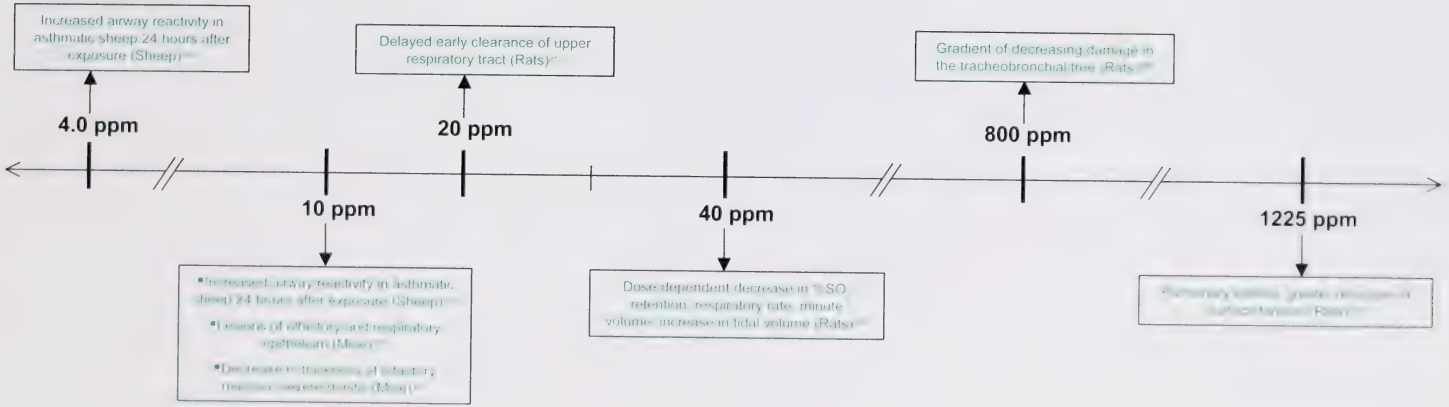

RESPIRATORY EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO SO_2: ANIMAL TOXICOLOGY STUDIES – *1 DAY TO 7 DAY EXPOSURES*

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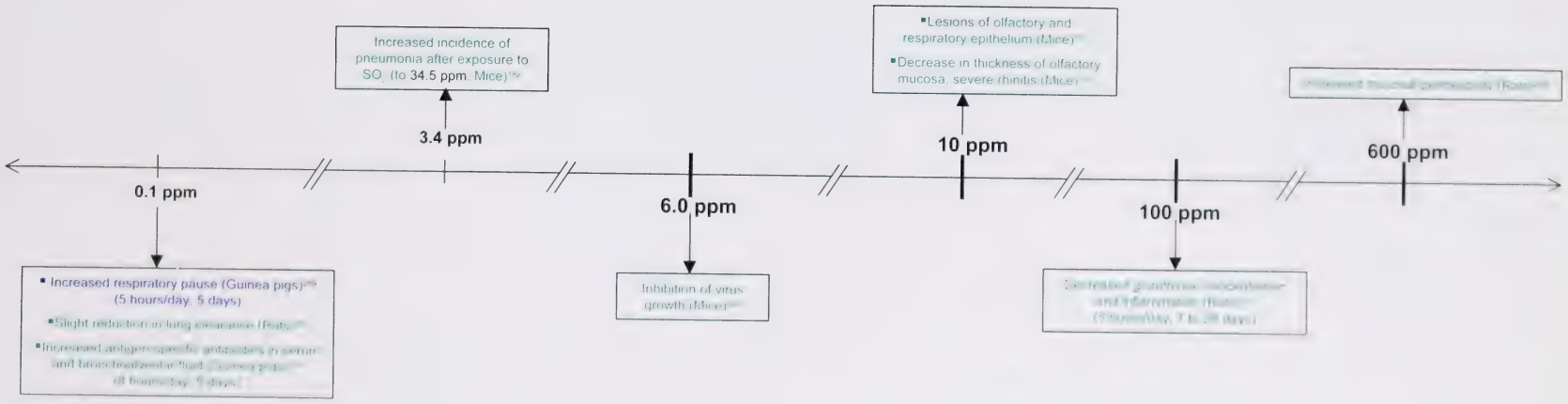
Green Font	= Moderate quality studies



RESPIRATORY EFFECTS ASSOCIATED WITH SHORT-TERM EXPOSURE TO SO_2: ANIMAL TOXICOLOGY STUDIES – *EXPOSURES GREATER THAN 7 DAYS AND UP TO 30 DAYS*

LEGEND	
Blue Font	= High quality studies
Green Font	= Moderate quality studies